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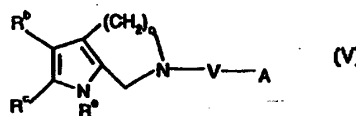
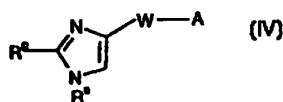
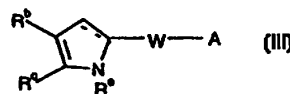
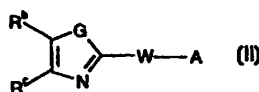
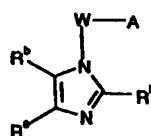
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: VITRONECTIN RECEPTOR ANTAGONISTS



## (57) Abstract

Compounds of formulae (I-V) are disclosed which are vitronectinreceptor antagonists and are useful in the treatment of osteoporosis.

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**TITLE**

Vitronectin Receptor Antagonists

**FIELD OF THE INVENTION**

5 This invention relates to pharmaceutically active compounds which inhibit the vitronectin receptor and are useful for the treatment of inflammation, cancer and cardiovascular disorders, such as atherosclerosis and restenosis, and diseases wherein bone resorption is a factor, such as osteoporosis.

**BACKGROUND OF THE INVENTION**

10 Integrins are a superfamily of cell adhesion receptors, which are transmembrane glycoproteins expressed on a variety of cells. These cell surface adhesion receptors include gpIIb /IIIa, the fibrinogen receptor, and  $\alpha_v\beta_3$ , the  
15 vitronectin receptor. The fibrinogen receptor gpIIb /IIIa is expressed on the platelet surface and it mediates platelet aggregation and the formation of a hemostatic clot at the site of a bleeding wound. Philips, *et al.*, *Blood.*, **1988**, *71*, 831. The vitronectin receptor  $\alpha_v\beta_3$  is expressed on a number of cells, including endothelial, smooth  
20 muscle, osteoclast, and tumor cells, and, thus, it has a variety of functions. The  $\alpha_v\beta_3$  receptor expressed on the membrane of osteoclast cells mediates the bone resorption process and contributes to the development of osteoporosis. Ross, *et al.*, *J. Biol. Chem.*, **1987**, *262*, 7703. The  $\alpha_v\beta_3$  receptor expressed on human aortic smooth  
25 muscle cells stimulates their migration into neointima, which leads to the formation of atherosclerosis and restenosis after angioplasty. Brown, *et al.*, *Cardiovascular Res.*, **1994**, *28*, 1815. Additionally, a recent study has shown that a  $\alpha_v\beta_3$  antagonist is able to promote tumor regression by inducing apoptosis of angiogenic blood vessels. Brooks, *et al.*, *Cell*, **1994**, *79*, 1157. Thus, agents that would block the vitronectin receptor would be useful in treating diseases mediated by this receptor, such as osteoporosis, atherosclerosis, restenosis and cancer.



The vitronectin receptor is known to bind to bone matrix proteins, such as osteopontin, bone sialoprotein and thrombospondin, which contain the tri-peptide Arg-Gly-Asp (or RGD) motif. Thus, Horton, *et al.*, *Exp. Cell Res.* **1991**, 195, 368, disclose that RGD-containing peptides and an anti-vitronectin receptor antibody (23C6) inhibit dentine resorption and cell spreading by osteoclasts. In addition, Sato, *et al.*, *J. Cell Biol.* **1990**, 111, 1713 disclose that echistatin, a snake venom peptide which contains the RGD sequence, is a potent inhibitor of bone resorption in tissue culture, and inhibits attachment of osteoclasts to bone. Fisher, *et al.*, *Endocrinology* **1993**, 132, 1411, has further shown that echistatin inhibits bone resorption *in vivo* in the rat. Bertolini *et al.*, *J. Bone Min. Res.*, 6, Sup. 1, S146, 252 have shown that cyclo-S,S-N $\alpha$ -acetyl-cysteinyl-N $\alpha$ -methyl-argininyl-glycyl-aspartyl-penicillamine inhibits osteoclast attachment to bone. EP 528 587 and 528 586 report substituted phenyl derivatives which inhibit osteoclast mediated bone resorption.

Alig *et al.*, EP 0 381 033, Hartman, *et al.*, EP 0 540,334, Blackburn, *et al.*, WO 93/08174, Bondinell, *et al.*, WO 93/00095, Blackburn, *et al.* WO 95/04057, Egbertson, *et al.*, EP 0 478 328, Sugihara, *et al.* EP 529,858, Porter, *et al.*, EP 0 542 363, and Fisher, *et al.*, EP 0 635 492 disclose certain compounds that are useful for inhibiting the fibrinogen receptor. It has now been discovered that certain appropriately substituted compounds are potent inhibitors of the vitronectin receptor. In particular, it has been discovered that such compounds are more potent inhibitors of the vitronectin receptor than the fibrinogen receptor and such compounds contain a fibrinogen receptor antagonist template.

## SUMMARY OF THE INVENTION

This invention comprises compounds of the formula (I)-(V) and (XXI)-(XXII) as described hereinafter, which have pharmacological activity for the inhibition of the vitronectin receptor and are useful in the treatment of inflammation, cancer and cardiovascular disorders, such as atherosclerosis and restenosis, and diseases wherein bone resorption is a factor, such as osteoporosis.

This invention is also a pharmaceutical composition comprising a compound according to formula (I)-(V) (XXI)-(XXII) and a pharmaceutically carrier.

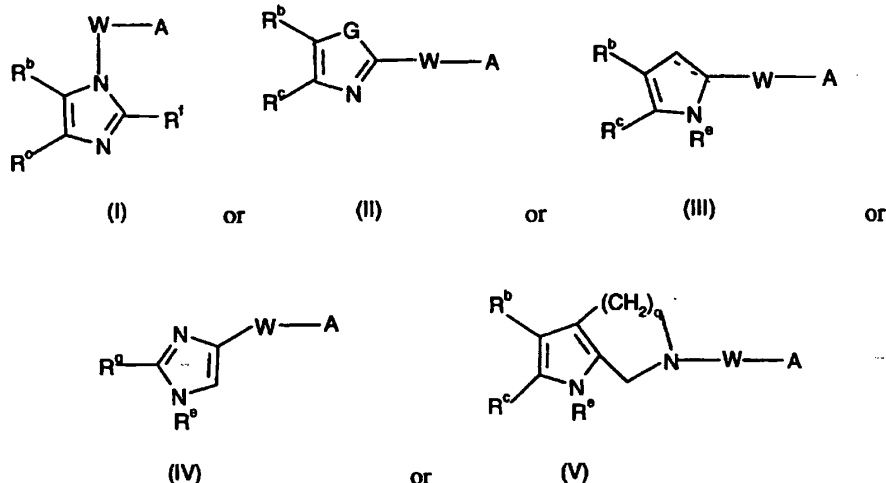
This invention is also a method of treating diseases which are mediated by the vitronectin receptor. In a particular aspect, the compounds of this invention are  
5 useful for treating atherosclerosis, restenosis, inflammation, cancer and diseases wherein bone resorption is a factor, such as osteoporosis.

### DETAILED DESCRIPTION

This invention comprises novel compounds which are more potent inhibitors  
10 of the vitronectin receptor than the fibrinogen receptor. The compounds of the instant invention comprise a fibrinogen receptor antagonist template that is linked to a nitrogen-containing five-membered ring, which is optionally fused to an aromatic six-membered ring. The fibrinogen receptor antagonist template is substituted by an aliphatic substituent which contains an acidic moiety. It is preferred that about  
15 fourteen intervening covalent bonds via the shortest intramolecular path will exist between the acidic group of the fibrinogen receptor antagonist template and the nitrogen of the optionally fused five-membered ring.

As used herein, the term "fibrinogen receptor antagonist template" means the core structure of a fibrinogen receptor antagonist, said core being substituted by an  
20 acidic group and said core being linked to an organic group substituted with a basic nitrogen moiety. A fibrinogen receptor antagonist is an agent that inhibits the binding of fibrinogen to the platelet-bound fibrinogen receptor GPIIb-IIIa. It is an object of this invention that a fibrinogen receptor antagonist is converted to a vitronectin receptor antagonist by replacing the organic group substituted with a  
25 basic nitrogen moiety in a fibrinogen receptor antagonist with an optionally fused nitrogen-containing five-membered ring, preferably an imidazole ring and, most preferably, a benzimidazole ring.

This invention comprises compounds of formula (I)-(V):



5 wherein:

W is -  $(CHR^g)_b-V'$  - or Ar;

A is a fibrinogen receptor antagonist template;

V' is  $CONR^{21}$  or  $NR^{21}CO$ ;

G is  $NR^e$ , S or O;

10  $R^g$  is H,  $C_{1-6}$ alkyl, Het- $C_{0-6}$ alkyl,  $C_{3-7}$ cycloalkyl- $C_{0-6}$ alkyl or Ar- $C_{0-6}$ alkyl;

$R^{21}$  is Het- $C_{0-6}$ alkyl- $U'$ - $C_{1-6}$ alkyl-,  $C_{3-7}$ cycloalkyl- $C_{0-6}$ alkyl- $U'$ - $C_{1-6}$ alkyl-, or Ar- $C_{0-6}$ alkyl- $U'$ - $C_{1-6}$ alkyl-;

$U'$  is  $CONR^f$  or  $NR^fCO$ ;

$R^f$  is H,  $C_{1-6}$ alkyl or Ar- $C_{1-6}$ alkyl;

15  $R^e$  is H,  $C_{1-6}$ alkyl, Ar- $C_{1-6}$ alkyl, Het- $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl- $C_{1-6}$ alkyl,

$(CH_2)_qOH$  or  $(CH_2)_kCO_2R^g$ ;

k is 0, 1 or 2;

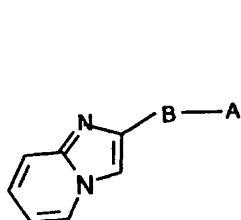
q is 1 or 2;

b is 0, 1 or 2;

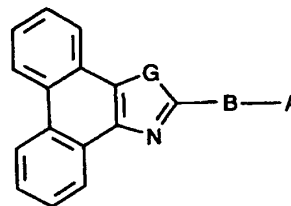
20  $R^b$  and  $R^c$  are independently selected from H,  $C_{1-6}$ alkyl, Ar- $C_{0-6}$ alkyl, Het- $C_{0-6}$ alkyl, or  $C_{3-6}$ cycloalkyl- $C_{0-6}$ alkyl, halogen,  $CF_3$ ,  $OR^f$ ,  $S(O)_kR^f$ ,  $COR^f$ ,  $NO_2$ ,  $N(R^f)_2$ ,  $CO(NR^f)_2$ ,  $CH_2N(R^f)_2$ , or  $R^b$  and  $R^c$  are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen

from halogen,  $\text{CF}_3$ ,  $\text{C}_{1-4}\text{alkyl}$ ,  $\text{OR}^f$ ,  $\text{S(O)}_k\text{R}^f$ ,  $\text{COR}^f$ ,  $\text{CO}_2\text{R}^f$ ,  $\text{OH}$ ,  $\text{NO}_2$ ,  $\text{N(R}^f)_2$ ,  $\text{CO(NR}^f)_2$ , and  $\text{CH}_2\text{N(R}^f)_2$ , or methylenedioxy; or a pharmaceutically acceptable salt thereof.

This invention also comprises compounds of formula (XXI)-(XXII):



(XXI)



(XXII)

5

wherein:

B is a linking moiety of the form  $-(\text{CHR}^g)_a\text{-U-}(\text{CHR}^g)_b\text{-V-}$ ;

A is a fibrinogen receptor antagonist template;

G is  $\text{NR}^e$ , S or O;

10  $\text{R}^g$  is H,  $\text{C}_{1-6}\text{alkyl}$ , Het- $\text{C}_{0-6}\text{alkyl}$ ,  $\text{C}_{3-7}\text{cycloalkyl-C}_{0-6}\text{alkyl}$  or Ar- $\text{C}_{0-6}\text{alkyl}$ ;

$\text{R}^k$  is  $\text{R}^g$ ,  $-\text{C(O)R}^g$ , or  $-\text{C(O)OR}^f$ ;

$\text{R}^i$  is H,  $\text{C}_{1-6}\text{alkyl}$ , Het- $\text{C}_{0-6}\text{alkyl}$ ,  $\text{C}_{3-7}\text{cycloalkyl-C}_{0-6}\text{alkyl}$ , Ar- $\text{C}_{0-6}\text{alkyl}$ ,  
Het- $\text{C}_{0-6}\text{alkyl-U'-C}_{1-6}\text{alkyl-}$ ,  $\text{C}_{3-7}\text{cycloalkyl-C}_{0-6}\text{alkyl-U'-C}_{1-6}\text{alkyl-}$ , or  
Ar- $\text{C}_{0-6}\text{alkyl-U'-C}_{1-6}\text{alkyl-}$  or  $\text{C}_{1-6}\text{alkyl}$ ;

15  $\text{R}^f$  is H,  $\text{C}_{1-6}\text{alkyl}$  or Ar- $\text{C}_{1-6}\text{alkyl}$ ;

$\text{R}^e$  is H,  $\text{C}_{1-6}\text{alkyl}$ , Ar- $\text{C}_{1-6}\text{alkyl}$ , Het- $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{3-7}\text{cycloalkyl-C}_{1-6}\text{alkyl}$ ,  
 $(\text{CH}_2)_q\text{OH}$  or  $(\text{CH}_2)_k\text{CO}_2\text{R}^g$ ;

U, U' and V independently are absent or CO,  $\text{CR}^g_2$ ,  $\text{C(=CR}^g_2)$ ,  $\text{S(O)}_k$ , O,  $\text{NR}^g$ ,

$\text{CR}^g\text{OR}^g$ ,  $\text{CR}^g(\text{OR}^k)\text{CR}^g_2$ ,  $\text{CR}^g_2\text{CR}^g(\text{OR}^k)$ ,  $\text{C(O)CR}^g_2$ ,  $\text{CR}^g_2\text{C(O)}$ ,  $\text{CON R}^i$

20

$\text{N R}^i\text{CO OC(O)}$ ,  $\text{C(O)O}$ ,  $\text{C(S)O}$ ,  $\text{OC(S)}$ ,  $\text{C(S)NR}^g$ ,  $\text{NR}^g\text{C(S)}$ ,  $\text{S(O)}_2\text{NR}^g$ ,

$\text{NR}^g\text{S(O)}_2$ ,  $\text{N=N}$ ,  $\text{NR}^g\text{NR}^g$ ,  $\text{NR}^g\text{CR}^g_2$ ,  $\text{NR}^g\text{CR}^g_2$ ,  $\text{CR}^g_2\text{O}$ ,  $\text{OCR}^g_2$ ,  $\text{C}\equiv\text{C}$ ,

$\text{CR}^g=\text{CR}^g$ , Ar or Het;

k is 0, 1 or 2;

q is 1 or 2;

a is 0, 1 or 2;

b is 0, 1 or 2;

$R^b$  and  $R^c$  are independently selected from H,  $C_{1-6}$ alkyl, Ar- $C_{0-6}$ alkyl, Het-

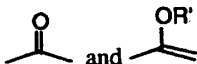
$C_{0-6}$ alkyl, or  $C_{3-6}$ cycloalkyl- $C_{0-6}$ alkyl, halogen,  $CF_3$ ,  $OR^f$ ,  $S(O)_kR^f$ ,  $COR^f$ ,

5  $NO_2$ ,  $N(R^f)_2$ ,  $CO(NR^f)_2$ ,  $CH_2N(R^f)_2$ , or  $R^b$  and  $R^c$  are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen,  $CF_3$ ,  $C_{1-4}$ alkyl,  $OR^f$ ,  $S(O)_kR^f$ ,  $COR^f$ ,  $CO_2R^f$  OH,  $NO_2$ ,  $N(R^f)_2$ ,  $CO(NR^f)_2$ , and  $CH_2N(R^f)_2$ ; or methylenedioxy;

10 or pharmaceutically acceptable salts thereof.

Preferably, U' is  $CONR^f$  or  $NR^fCO$ .

Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as

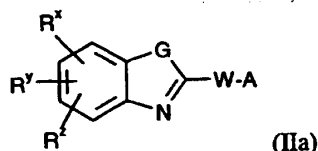
keto-enol tautomers, such as , and each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or locked in one form by appropriate substitution with  $R'$ .

25 The compounds of formula (I) - (V) and (XXI) - (XXII) inhibit the binding of vitronectin and other RGD-containing peptides to the vitronectin ( $\alpha_v\beta_3$ ) receptor. Inhibition of the vitronectin receptor on osteoclasts inhibits osteoclastic bone resorption and is useful in the treatment of diseases wherein bone resorption is associated with pathology, such as osteoporosis. Additionally, since the compounds

of the instant invention inhibit vitronectin receptors on a number of different types of cells, said compounds would be useful in the treatment of inflammation and cardiovascular diseases, such as atherosclerosis and restenosis, and would be useful as anti-metastatic and antitumor agents.

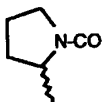
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In a particular embodiment, the compounds of this invention are of the formula (II), wherein  $R^b$  and  $R^c$  are joined to form an aromatic ring containing up to two nitrogen atoms. In a preferred embodiment  $R^b$  and  $R^c$  are joined to form an optionally substituted phenyl ring according to formula (IIa):



10

wherein G is  $N-R^d$ , S, CH or O.

Suitably W is  $-(CH_2)_nNR^iCO-$  or , or, when G is CH, W is

$-CH_2CH_2NR^iCO-$  wherein  $R^i$  is a methylene group attached to G.

Preferably W is  $-CH_2CH_2NR^iCO-$ .

15

Suitably  $R^i$  is H,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, Ar or  $C_{1-6}$ alkyl substituted by one to three groups chosen from halogen, CN,  $NR^j_2$ ,  $OR^k$ ,  $SR^k$ ,  $CO_2R^k$ , and  $CON(R^k)_2$ , Ar, Het or  $C_{3-7}$ cycloalkyl. In particular,  $R^i$  is H, methyl, butyl, cyanomethyl, carboxymethyl, phenylethyl or benzimidazolylmethyl.

Suitably  $R^x$ ,  $R^y$  and  $R^z$  are independently chosen from  $C_{1-6}$ alkyl, methoxy, nitro, trifluoromethyl, fluoro, chloro, amino or  $R^x$  and  $R^y$  are adjacent to one another and are joined to form a methylenedioxy group.

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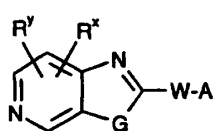
Preferably G is  $NR^d$ .

Suitably  $R^d$  is H,  $C_{1-4}$ alkyl, Ar, Het or  $C_{1-4}$ alkyl substituted by Ar or Het.

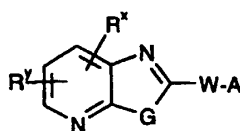
More suitably,  $R^d$  is H, methyl or benzimidazolylmethyl.

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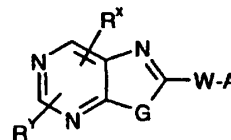
In another specific embodiment,  $R^b$  and  $R^c$  form a six membered aromatic ring containing one or two nitrogen atoms according to formulas (IIb-d):



(IIb)



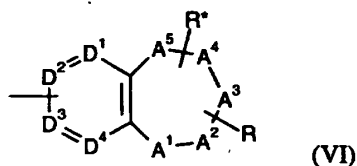
(IIc)



(IIId)

5 wherein G,  $R^x$  and  $R^y$  are as above for formula (IIa).

Specifically, the compounds of this invention are comprised of a nitrogen-containing optionally fused five-membered ring, a linking group W, and a fibrinogen receptor antagonist template A. In particular, the fibrinogen receptor antagonist template A is as defined in Bondinell, et al., WO 93/00095, published January 7,  
10 1993, of the sub-formula (VI):



(VI)

$A^1$  to  $A^5$  form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from  
15 the group of O, S and N wherein S and N may be optionally oxidized;

$D^1$  to  $D^4$  form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

R is at least one substituent chosen from the group of  $R^7$ , or  $Q-C_{1-4}$ alkyl,  $Q-C_{2-4}$ alkenyl,  $Q-C_{2-4}$ alkynyl, optionally substituted by one or more of =O,  $R^{11}$  or  
20  $R^7$ ;

$R^*$  is H,  $Q-C_{1-6}$ alkyl,  $Q-C_{1-6}$ oxoalkyl,  $Q-C_{2-6}$ alkenyl,  $Q-C_{3-4}$ oxoalkenyl,  $Q-C_{3-4}$ oxoalkynyl,  $Q-C_{2-4}$ alkynyl,  $C_{3-6}$ cycloalkyl, Ar or Het, optionally substituted by one or more of  $R^{11}$ ;

Q is H,  $C_{3-6}$ cycloalkyl, Het or Ar;

- $R^7$  is  $-\text{COR}^8$ ,  $-\text{COCR}_2\text{R}^9$ ,  $-\text{C(S)R}^8$ ,  $-\text{S(O)}_m\text{OR}'$ ,  $-\text{S(O)}_m\text{NR}'\text{R}''$ ,  $-\text{PO(OR}')$ ,  $-\text{PO(OR}')}_2$ ,  $-\text{B(OR}')}_2$ ,  $-\text{NO}_2$  and Tet;
- $R^8$  is  $-\text{OR}'$ ,  $-\text{NR}'\text{R}''$ ,  $-\text{NR}'\text{SO}_2\text{R}'$ ,  $-\text{NR}'\text{OR}'$ ,  $-\text{OCR}'_2\text{C(O)OR}'$ ,  $-\text{OCR}'_2\text{OC(O)-R}'$ ,  $-\text{OCR}'_2\text{C(O)NR}'_2$ ,  $\text{CF}_3$  or  $\text{AA}^1$ ;
- 5  $R^9$  is  $-\text{OR}'$ ,  $-\text{CN}$ ,  $-\text{S(O)}_n\text{R}'$ ,  $\text{S(O)}_m\text{NR}'_2$ ,  $-\text{C(O)R}'\text{C(O)NR}'_2$  or  $-\text{CO}_2\text{R}'$ ;
- $R^{11}$  is H, halo,  $-\text{OR}^{12}$ ,  $-\text{CN}$ ,  $-\text{NR}'\text{R}^{12}$ ,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $\text{CF}_3\text{S(O)}_n$ ,  $-\text{CO}_2\text{R}'$ ,  $-\text{CONR}'_2$ ,  $\text{Q-C}_{0-6}\text{alkyl-}$ ,  $\text{Q-C}_{1-6}\text{oxoalkyl-}$ ,  $\text{Q-C}_{2-6}\text{alkenyl-}$ ,  $\text{Q-C}_{2-6}\text{alkynyl-}$ ,  $\text{Q-C}_{0-6}\text{alkyloxy-}$ ,  $\text{Q-C}_{0-6}\text{alkylamino-}$  or  $\text{Q-C}_{0-6}\text{alkyl-S(O)}_n$ ;
- $R^{12}$  is  $\text{R}'$ ,  $-\text{C(O)R}'$ ,  $-\text{C(O)NR}'_2$ ,  $-\text{C(O)OR}^{15}$ ,  $-\text{S(O)}_m\text{R}'$  or  $\text{S(O)}_m\text{NR}'_2$ ;
- 10  $R^{13}$  is  $\text{R}'$ ,  $-\text{CF}_3$ ,  $-\text{SR}'$ , or  $-\text{OR}'$ ;
- $R^{14}$  is  $\text{R}'$ ,  $\text{C(O)R}'$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $\text{SO}_2\text{R}'$  or  $\text{C(O)OR}^{15}$ ;
- $R^{15}$  is H,  $\text{C}_{1-6}\text{alkyl}$  or  $\text{Ar-C}_{0-4}\text{alkyl}$ ;
- $\text{R}'$  is H,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{3-7}\text{cycloalkyl-C}_{0-4}\text{alkyl}$  or  $\text{Ar-C}_{0-4}\text{alkyl}$ ;
- $\text{R}''$  is  $\text{R}'$ ,  $-\text{C(O)R}'$  or  $-\text{C(O)OR}^{15}$ ;
- 15  $\text{R}'''$  is  $\text{R}''$  or  $\text{AA}^2$ ;
- $\text{AA}^1$  is an amino acid attached through its amino group and having its carboxyl group optionally protected, and  $\text{AA}^2$  is an amino acid attached through its carboxyl group, and having its amino group optionally protected;
- $m$  is 1 or 2;
- 20  $n$  is 0 to 3;
- $p$  is 0 or 1; and
- $t$  is 0 to 2; or
- pharmaceutically acceptable salts thereof.
- 25 With reference to formula (VI), suitably,
- $\text{A}^1$  is  $\text{CR}^1\text{R}^1$ ,  $\text{CR}^1$ ,  $\text{NR}^1$ , N, O or  $\text{S(O)}_x$ ;
- $\text{A}^2$  is  $\text{CR}^2\text{R}^2$ ,  $\text{CR}^2$ ,  $\text{NR}^2$ ;
- $\text{A}^3$  is  $\text{CR}^3\text{R}^3$ ,  $\text{CR}^3$ ,  $\text{NR}^3$ , N, O or  $\text{S(O)}_x$ ;



$A^4$  is  $CR^4R^{4'}$ ,  $CR^4$ ,  $NR^4$ , or  $N$ ;

$A^5$  is  $CR^5R^{5'}$ ,  $CR^5$ ,  $NR^5$ ,  $N$ ,  $O$  or  $S(O)_x$ ;

$D^1$ - $D^4$  are  $CR^{11}$ ,  $CR^6$  or  $N$ ;

$R^1$  and  $R^{1'}$  are  $R^*$  or  $R$ , or together are  $=O$ ;

5  $R^2$  and  $R^{2'}$  are  $R^*$ ,  $R$  or  $=O$ ;

$R^3$  and  $R^{3'}$  are  $R^*$ ,  $R$  or  $=O$ ;

$R^4$  and  $R^{4'}$  are  $R^*$ ,  $R$  or  $=O$ ;

$R^5$  and  $R^{5'}$  are  $R^*$ ,  $R$  or  $=O$ ; and

$x$  is 0 to 2.

10 More suitably,  $A^1$  is  $CR^1R^{1'}$ ,  $CR^1$ ,  $NR^1$ ,  $N$ ,  $O$  or  $S$ ;  $A^2$  is  $CR^2R^{2'}$ ,  $NR^2$  or  $CR^2$ ;  $A^3$  is  $CR^3R^{3'}$ ;  $A^4$  is  $CR^4R^{4'}$ ,  $CR^4$ ,  $NR^4$ , or  $N$ ;  $A^5$  is  $CR^5R^{5'}$ ,  $CR^5$ ,  $NR^5$ ,  $N$ ,  $O$ ;  $D^1 - D^4$  are  $CH$ ;  $R^2$  or  $R^4$  are  $R$ ;  $R^3, R^{3'}$  and  $R^5, R^{5'}$  are  $=O$  or  $R^*, H$ .

Preferably,  $A^1$  is  $CHR^1$ ,  $CR^1$ ,  $NR^1$ ,  $N$  or  $S$ ;  $A^2$  is  $CR^2$  or  $CR^2R^{2'}$ ;  $A^3$  is  $CR^3R^{3'}$ ;  $A^4$  is  $CR^4R^{4'}$  or  $NR^4$ ;  $A^5$  is  $CR^5R^{5'}$ , and  $D^1 - D^4$  are  $CH$ .

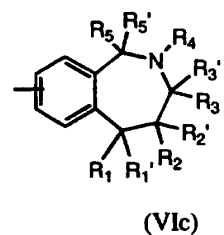
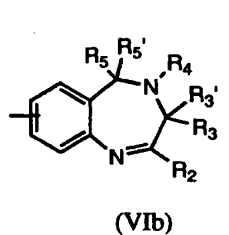
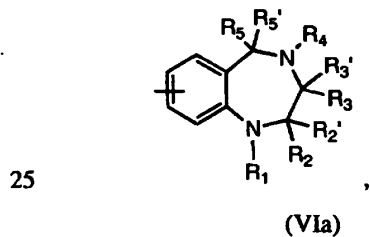
15 In one embodiment,  $A^1$  is  $CR^1$ ,  $A^2$  is  $CR^2$ ,  $A^3$  is  $C=O$ ,  $A^4$  is  $NR^4$  and  $A^5$  are  $CHR^5$ .

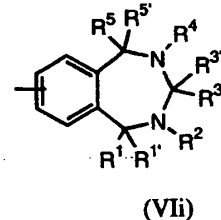
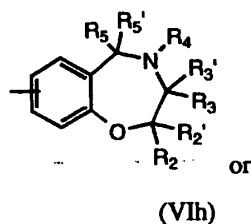
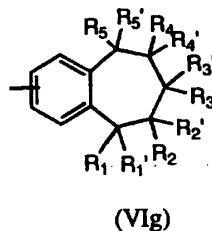
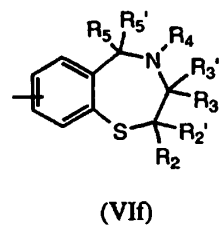
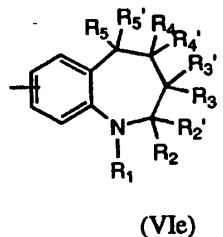
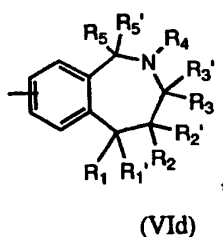
In another embodiment,  $A^1$  is  $NR^1$ ,  $A^2$  is  $CHCR^2$ ,  $A^3$  is  $CR^3R^{3'}$ ,  $A^4$  is  $NR^4$ , and  $A^5$  are  $C=O$ .

In yet another embodiment,  $A^1$  and  $A^4$  are  $C=O$ ,  $A^2$  is  $NR^2$ ,  $A^3$  is  $CHR^{3'}$  and  
20  $A^5$  is  $NR^5$ .

In a preferred embodiment,  $A^1$  is  $NR^1$ ,  $A^2$  is  $CHR^2$ ,  $A^3$  is  $C=O$ ,  $A^4$  is  $NR^4$  and  $A^5$  is  $CHR^5$ .

Representative sub-formulas of (VI) are given by each of formulas (VIa)-  
(VIi) below:





5

Specific embodiments of this invention wherein the fibrinogen receptor antagonist template A is of the sub-formula (VI) are named in the Examples.

Preferred compounds of this invention are:

- 10 5-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-aminoacetic acid;  
 (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;  
 15 (S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;  
 (S)-2,3,4,5-Tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;  
 20 (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;  
 (S)-2,3,4,5-Tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

- S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(4-phthalimidobutyl)-1H-1,4-benzodiazepine-2-acetic acid;
- 4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetic acid;
- 4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]phenylacetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetamide;
- (±)-2,3,4,5-Tetrahydro-7-[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

- (±)-2,3,4,5-Tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;
- 5 (S)-2,3,4,5-Tetrahydro-7-[[[(5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;
- 10 (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-4-methyl-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;
- 15 (±)-4-[4-[[[(1H-Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoic acid;
- (±)-3-[[[4-(4-Azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoic acid;
- 20 (S)-2,3,4,5-Tetrahydro-7-[[[1-(2-hydroxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- 25 (S)-2,3,4,5-Tetrahydro-7-[[[(4-aminobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate;
- 30

- (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester;
- 2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;
- (±)-N-[2-(Aminomethyl)-4-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]aspartic acid;
- (±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-4-[4-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate;
- (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(2-carboxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;
- Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate;
- 2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetic acid;

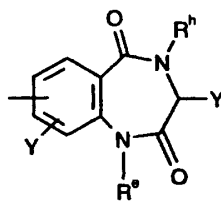
- 2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-5-[[2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-yl]methyl]tetrazole;
- (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-(N-hydroxy)acetamide;
- Ethyl (±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate;
- (±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoic acid;
- (±)-2,3,4,5-Tetrahydro-7-[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;
- 2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;
- 2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid; and

(±)-7-[[[(4,5-Dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;  
or pharmaceutically acceptable salts thereof.

The most preferred fibrinogen receptor antagonist template is of the sub-  
5 formula (VIa), wherein  $CR^2R^{2'}$  is  $CHCH_2CO_2H$ ,  $CR^3R^{3'}$  is  $C=O$ , and  $CR^5R^{5'}$  is  $CH_2$ . Vitronectin fibrinogen receptor antagonism is particularly pronounced when the A-W- substituent is attached to the 7-position of the 3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine ring system.

In the formula below the definitions for the substituents are as defined in  
10 formulas (I)-(V) and (XX)-(XXI), unless specified otherwise.

Another embodiment of a preferred fibrinogen receptor template A is represented by the 1,4-benzodiazepine 2,5-dione of sub-formula (VII);



(VII)

15 wherein:

Y is H,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkoxycarbonyl, F, Cl, Br, I,  $CF_3$ ,  $OR^f$ ,  $S(O)_kR^f$ ,  $COR^f$ ,  $NO_2$ ,  $N(R^f)_2$ ,  $CO(NR^f)_2$ ,  $CH_2N(R^f)_2$ , methylenedioxy, CN,  $CO_2R^f$ ,  $OC(O)R^f$ , or  $NHC(O)R^f$ ; and  
 $R^h$  is  $(CH_2)_qCO_2R^f$ .

20

The preparation and the use of this sub-structure in preparing fibrinogen receptor antagonists of this sub-formula is detailed in Bondinell, et al., WO 93/00095 published January 7, 1993 and Blackburn, et al., WO 93/08174, published April 29, 1993.

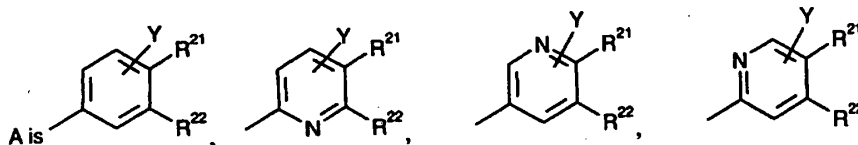
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Table I, below, summaries other preferred fibrinogen receptor templates that are included within the scope of the present invention. Such templates are:

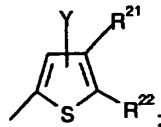
Table I

(VIII)

5



or



wherein:

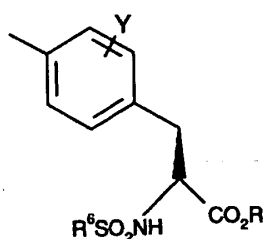
- 10  $R^{21}$  and  $R^{22}$  independently are H or  $-Z-CO_2R^f$  or  $Z-CON(R^f)_2$  with the proviso that one of  $A^1$  or  $A^2$  is  $-Z-CO_2R^f$  or  $Z-CON(R^f)_2$ ;

$Z$  is  $-CH_2-$ ,  $-O(CH_2)_q-$ ,  $-NR^f(CH_2)_q-$ ,  $-S(CH_2)_q-$ ,  $-CH_2CH_2-$ ,  $-CH(CH_3)CH_2-$ ,  $-(CH_2)_3-$ ,  $-CH=CH-$ ,  $-C(CH_3)=CH-$ ,  $CH_2-CH=CH-$  or  $CH=CHCH_2-$ ; and

$Y$  is H,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkoxycarbonyl, F, Cl, Br, I,  $CF_3$ ,  $OR^f$ ,  $S(O)_kR^f$ ,

- 15  $COR^f$ ,  $NO_2$ ,  $N(R^f)_2$ ,  $CO(NR^f)_2$ ,  $CH_2N(R^f)_2$ , methylenedioxy or  $Z-COR^f$ ,  
in Alig, et al., EP 0 381 033, published August 8, 1990.

(IX)



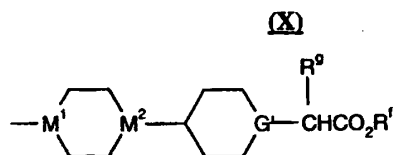
- 20 wherein:



$R^6$  is aryl,  $C_{1-10}$ alkyl,  $C_{3-6}$ cycloalkyl,  $C_{4-10}$ aralkyl,  $C_{1-10}$ alkoxyalkyl,  $C_{1-10}$ alkaryl,  $C_{1-10}$ alkylthioalkyl,  $C_{1-10}$ alkoxythioalkyl,  $C_{1-10}$ alkylamino,  $C_{4-10}$ aralkylamino,  $C_{1-10}$ alkanoylamino,  $C_{4-10}$ aralkanoylamino,  $C_{1-10}$ alkanoyl,  $C_{4-10}$ aralkanoyl, or  $C_{1-10}$ carboxyalkyl; and

- 5         $Y$  is H,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkoxycarbonyl, F, Cl, Br, I,  $CF_3$ ,  $OR^f$ ,  $S(O)_kR^f$ ,  $COR^f$ ,  $NO_2$ ,  $N(R^f)_2$ ,  $CO(NR^f)_2$ ,  $CH_2N(R^f)_2$ , methylenedioxy, CN,  $CO_2R^f$ ,  $OC(O)R^f$ , or  $NHC(O)R^f$ ,  
in Egbertson, et al., EP 0 478 328, published April 1, 1992.

10



wherein:

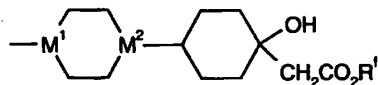
$M^1$  is CH or N;

$M^2$  is CH or N, with the proviso that when  $M^1$  is CH,  $M^2$  is N; and

- 15         $G'$  is N or  $N^{\oplus}R''$ ,

in Eldred, et al., EP 0542 363, published May 19, 1993.

(XI)



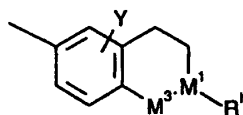
- 20        wherein:

$M^1$  is CH or N; and

$M^2$  is CH or N, with the proviso that when  $M^1$  is CH,  $M^2$  is N,

in Porter, et al., EP 0 537 980, published April 21, 1993.

(XII)



wherein:

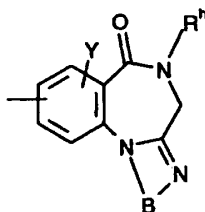
 $M^1$  is CH or N;

- 5        Y is H,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkoxycarbonyl, F, Cl, Br, I,  $CF_3$ ,  $OR^f$ ,  $S(O)_kR^f$ ,  $COR^f$ ,  $NO_2$ ,  $N(R^f)_2$ ,  $CO(NR^f)_2$ ,  $CH_2N(R^f)_2$ , methylenedioxy, CN,  $CO_2R^f$ ,  $OC(O)R^f$ , or  $NHC(O)R^f$ ;

 $D^3$  is  $CH_2$  or  $C=O$ ; and $R^h$  is  $(CH_2)_qCO_2R^f$ ,

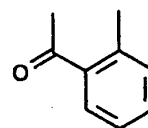
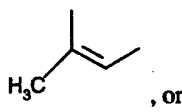
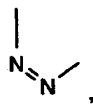
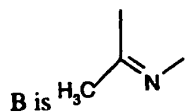
- 10    in Klinnick, et al., EP 0 635,492, published January 25, 1995.

(XIII)



wherein:

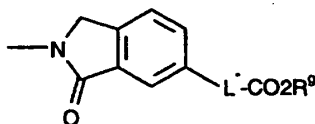
- 15        Y is H,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkoxycarbonyl, F, Cl, Br, I,  $CF_3$ ,  $OR^f$ ,  $S(O)_kR^f$ ,  $COR^f$ ,  $NO_2$ ,  $N(R^f)_2$ ,  $CO(NR^f)_2$ ,  $CH_2N(R^f)_2$ , methylenedioxy, CN,  $CO_2R^f$ ,  $OC(O)R^f$ , or  $NHC(O)R^f$ ;

 $R^h$  is  $(CH_2)_nCO_2R^f$ ; and

in Blackburn, et al., WO 95/04057, published February 9, 1995.

20

(XIV)

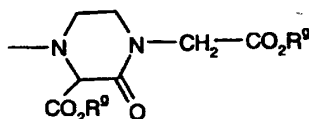


wherein:

$L^*$  is  $-C(O)NR^g-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  $NR^g-(CH_2)_q-$ ,  $-O-(CH_2)_q-$ , or  $S(O)_k-(CH_2)_q-$ ,

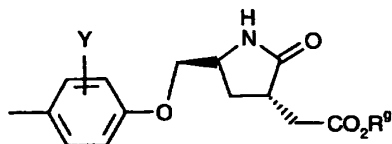
5 in Hartman, et al., EP 0 540 331, published May 5, 1993.

(XV)



in Sugihara, et al., EP 0 529,858, published March 3, 1993.

(XVI)



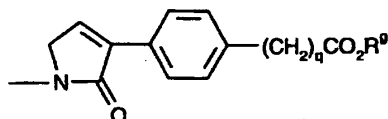
10

wherein:

Y is H,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkoxycarbonyl, F, Cl, Br, I,  $CF_3$ ,  $OR^f$ ,  $S(O)_kR^f$ ,  $COR^f$ ,  $NO_2$ ,  $N(R^f)_2$ ,  $CO(NR^f)_2$ ,  $CH_2N(R^f)_2$ , methylenedioxy, CN,  $CO_2R^f$ ,  $OC(O)R^f$ , or  $NHC(O)R^f$ ,

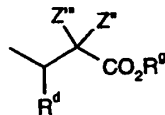
15 in Himmeisbach, et al., EP 0 483 667, published May 6, 1992.

(XVII)



in Linz, et al., EP 0 567 968, published November 3, 1993.

(XVIII)



wherein:

$R^d$  is Het- $C_{0-6}$ alkyl; and

$Z''$ ,  $Z'''$  independently are hydrogen,  $C_{1-4}$ alkyl, halo,  $OR^f$ , CN,  $S(O)_kR^f$ ,

5  $CO_2R^f$ , or OH,

in Bovy, et al., EP 0 539 343, published April 28, 1993.

Compounds of this invention comprising specific fibrinogen templates are named in the examples. These examples illustrate the invention, but do not limit the scope of the invention.

10

The above descriptions of fibrinogen receptor templates for use in the present invention were taken from pending published patent applications. Reference should be made to such patent applications for their full disclosures, including the methods of preparing said templates and specific compounds using said templates, the entire disclosure of such patent applications being incorporated herein by reference.

15

Table II, below, describes other fibrinogen receptor antagonists, whose core structures would be useful in carrying out the instant invention. Reference should be made to the patent applications and other publications for their full disclosures, including the methods of preparing said templates and specific compounds using said templates, the entire disclosure of the noted patent applications and other publications being incorporated herein by reference. Since it is contemplated that any fibrinogen receptor antagonist that is linked to an optionally fused nitrogen-containing five-membered ring will possess the novel utility described herein, the list below does not limit the scope of the present invention.

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Table II**Adir et Compagnie**

FR 928004, June 30, 1992, Fauchere, J. L., et al.

- 5 EP 0578535, June 29, 1993, Fauchere, J-L, et al.: Describes X-RGDW-OH analogs,  
where X contains a cationic amine.

CA 2128560, Jan. 24, 1995, Godfroid, J-J, et al., substituted piperazines.

**Asahi Breweries, Ltd.**

JP 05239030, Sep. 17, 1993, aminomethyltetrahydroisoquinolines.

10

**Asahi Glass**

WO 90/02751, Ohba, M. et al.: Sept. 8, 1989: Describes cyclic RGD-containing  
peptides.

WO 90/115950, Mar. 22, 1990, Ohba, M., et al.

- 15 EP 0406428, 1/9/91: Describes cyclic RGD-containing peptides  
WO 92/09627, Isoai, A. et al.: Nov. 29, 1991: Describes cyclic RGD-containing  
peptides.

**Cassella AG**

- 20 DE 4207254, (Der 93-289298/37) Mar. 7, 1992, Zoller, G., et al.: Describes  
guanidinopropyl-4-oxo-2-thioimidazolidin-3-yl-Asp-X analogs  
EP 93904010, Feb. 24, 1993, Zoller, G., 4-oxo-2-Thioxoimidazolidine Derivatives.  
EP 0565896, Mar. 18, 1993, Klinger, O, et al.: Describes  
guanidinoethylphenyloxyacetyl-Asp-X analogs.
- 25 EP 0566919, (Der 93-338002/43) Apr. 3, 1993, Zoller, G., et al.: Describes  
guanidinopropyl-4-oxo-2-thioimidazolidin-3-yl-Asp-X analogs.  
EP 580008, (Der 94-027663/04) July 6, 1993, Zoller, G., et al.: Describes 5-m-  
guanidinophenyl-2,4-dioxoimidazolidin-3yl)acetyl-Asp-Phg.  
DE 224414, July 6, 1993, Zoller, G., et al.: Describes 5-m-guanidinophenyl-2,4-  
30 dioxoimidazolidin-3yl)acetyl-Asp-Phg.

- EP 584694, (Der 94-067259/09) Apr. 2, 1994, Zoller, G., et al.: Describes 5-m-guanidinophenyl-2,4-dioxoimidazolidin-3yl)acetyl-Asp-Phg.
- DE 4301747, (Der 94-235891/29) Jul. 28, 1994, Zoller, G., et al.: Describes 5-m-guanidinophenyl-2,4-dioxoimidazolidin-3yl)acetyl-Asp-Phg analogs.
- 5 DE 4308034, (Der 94-286666/36) Sept. 15, 1994, Klinger, O. et al.: Describes 5-m-guanidinophenyl-2,4-dioxoimidazolidin-3yl)acetyl-Asp-Phg analogs.
- DE 4309867, Sept. 29, 1994, Klingler, O, et al.: Describes 5-m-guanidinophenyl-2,4-dioxoimidazolidin-3yl)acetyl-Asp-Phg.
- 10 **Chiron**
- WO 93/07169, (Der 93-134382/16), Mar. 15, 1993, Devlin, J. J., et al.: Describes RGD peptides.
- Ciba Geigy**
- 15 EP 0452210, (Der 91-305246/42) Apr. 5, 1990, describes aminoalkanoyl-GDF analogs.
- EP 0452257, Mar. 26, 1991, Allen, M. C., et al.: Describes aminoalkanoylAsp-Phe analogs.
- 20 **COR Therapeutics**
- WO 90/15620, June 15, 1990: Describes cyclic RGD-containing peptides.
- EP 0477295, Apr. 1, 1992: Scarborough, R. M. et al.
- WO 92/08472, May 29, 1992, Scarborough, R. M. et al.
- WO 93/223356, April 27, 1993, Swift, R. L., et al.: Describes cyclic RGD-
- 25 containing peptides.
- EP 0557442, Sept. 1, 1993, Scarborough, R. M., et al.
- Scarborough, R. M.; Rose, J. W.; Hsu, M. A.; Phillips, D. R.; Fried, V. A.; Campbell, A. M.; Nunnizzi, L.; Charo, I. F., Barbourin, A GPIIb-IIIa-Specific Integrin Antagonist from the Venom of Sistrurus M. Barbouri, *J. Biol. Chem.* , 266, 9359, 1991.
- 30

**Daiichi Pharm Co Ltd.**

JP 05078344-A, (Der 93-140339/17) Mar. 30, 1993: Describes Bis-amidinoheterocycles, eg. benzofurans.

**5 DuPont Merck**

WO 93/07170, Apr. 15, 1993: Describes cyclic-RGD-containing peptides.

WO 94/11398, May 26, 1994: Wells, G. J. et al. Describes cyclic RGD containing peptides.

IL 109237, Jul. 31, 1994.

10 WO 94/22909, (Der 94-333113/41) Oct. 13, 1994: DeGrado W. F., et al.

WO 94/22910, (Der 94-333114/41) Oct. 13, 1994: DeGrado W. F., et al. Prodrugs.

WO 94/22494, (Der 94-332838/41) Oct. 13, 1994: DeGrado W. F., et al. Cyclic peptides

EP 625164, Nov. 23, 1994: Degrado, W. F., et al. Cyclic peptides.

15 Mousa, S. A.; Bozarth, J. M.; Forsythe, M. S.; Jackson, S. M.; Leamy, A.; Diemer, M. M.; Kapil, R. P.; Knabb, R. M.; Mayo, M. C.; Pierce, S. K.; al., e., Antiplatelet and Antithrombotic Efficacy of DMP 728, a Novel Platelet GPIIb/IIIa Receptor Antagonist, *Circulation*, 89, 3, 1994.

Jackson, S.; DeGrado, W.; Dwivedi, A.; Parthasarathy, A.; Higley, A.; Krywko, J.;

20 Rockwell, A.; Markwalder, J.; Wells, G.; Wexler, R.; Mousa, S.; Harlow, R., Template-Constrained Cyclic Peptides: Design of High-Affinity Ligands for GPIIb/IIIa, *J. Amer. Chem. Soc.*, 116, 3220, 1994.

**Ellem Ind Farma Spa**

25 GB 2207922, Aug. 3, 1988, describes linear RGD analogs.

**Farmitalia Erba SRL Carlo**

EP 611765 (Der 94-265375/33), Aug 24, 1994: Cozzi, P., et al. Describes 5-(2-

30 pyrazinylmethyl-2-imidazol-1-yl)-1-cyclohexylethylidene)aminoxypentanoic acid.

**Fuji Photo Film**

- JP 04208296-A (Der. 92-303598/38), Nov. 30, 1990, Describes RGD peptides.
- JP 04213311-A (Der. 92-305482/38), Nov. 27, 1990, Describes multimeric RGD peptides.
- 5 JP 04217693-A, (Der 92-312284/38), Oct. 23, 1990, Describes multimeric RGD peptides.
- JP 04221394-A (Der. 92-313678/38), Oct. 26, 1990, Describes multimeric RGD peptides.
- JP 04221395-A (Der. 92-313679/38), Oct. 26, 1990, Describes multimeric RGD peptides.
- 10 JP 04221396-A (Der. 92-313680/38), Oct. 26, 1990, Describes multimeric RGD peptides.
- JP 04221397-A (Der. 92-313681/38), Dec. 20, 1990, Describes multimeric RGD peptides.
- 15 EP 0482649 A2, April 29, 1992, Kojima, M. et al.: Describes RGD peptides.
- EP 0488258A2, June 3, 1992, Komazawa, H., et al: Describes RGD peptides.
- EP 503301-A2, Feb. 14, 1991, Kitaguchi, H. et al.: Describes RGD peptides.
- JP 05222092, May 21, 1993, Nishikawa, N., et al.: Describes Linear X-RGDS.
- JP 06239885, (Der 94-313705/39) , Aug 30, 1993, Nishikawa, N. et al.: Describes multimeric RGD peptides.
- 20 WO 9324448, (Der 93-405663/50), Dec. 9, 1993, Nishikawa, N., et al.: Describes multimeric retro-inverse RGD peptides.
- JP 06228189, (Der 94-299801/37), Aug. 16, 1994. Describes RGD peptides.
- EP 619118, (Der 94-311647/39) , Oct. 12, 1994, Nishikawa, N. et al.: Describes linear RGD peptides.
- 25

**Fujisawa**

- EP 0513675, May 8, 1992, N. Umekita, et al.: Describes amidinophenylalkanoic acid-Asp-Val-OH analogs.
- 30 WO 9409030-A1, Apr. 28, 1994, Takasugi, H., et al.: Describes Amidinophenylbutanoic acid-Asp-Val-OH analogs.



EP 0513675, (Der 92-383589/47): Describes Amidinophenyloxybutyryl-Asp-Val  
analogs.

WO 9500502, Jan, 5, 1995, Oku, T., et al.,: Describes "aminopiperazine  
derivatives."

5 FR 144633: *Thromb Haem.* 69, 706, 1993.

Cox, D.; Aoki, T.; Seki, J.; Motoyama, Y.; Yoshida, K., Pentamidine: A Specific  
Nonpeptide GPIIb/IIIa Antagonist, *Thromb. Haem.* , 69, 707, 1993.

#### Genentech

10 WO 90/15072 (Der 91007159): Describes RGD-containing peptides:

WO 91/01331 (Der 91058116), July 5, 1990, P. L. Barker, et al.: Describes cyclic  
RGD-containing peptides

WO 91/04247, Sept. 24, 1990, T. R. Webb: Describes (guanidinoalkyl)Pro-GD  
analogs.

15 WO 91/11458 (Der 91252610), Jan. 28, 1991, P. L. Barker, et al.: Describes cyclic  
RGD-containing peptides

WO 92/07870, Oct. 24, 1991 J. P. Burnier, et al.: Describes cyclic RGD-  
containing peptides.

WO 92/17492, Oct. 15, 1992, Burnier, J. P. et al.: Describes cyclic RGD-containing  
20 peptides.

CA 2106314, Oct. 6, 1992, Burnier, J. P. et al.

WO 93/08174, Oct. 15, 1991, B. K. Blackburn, et al.: Describes 2,5-dioxo-1,4-  
benzodiazepines.

CA 2106314, Oct. 6, 1992, Burnier, J. P., et al.

25 EP 0555328, Aug. 18, 1993, J. P. Burnier, et al.

WO 95/04057, Feb. 9, 1995, Blackburn, B. K., et al.: Describes 1,4-benzodiazepines  
containing a heterocyclic at positions 1,2.

Scarborough, R. M., Naughton, M. A., Teng, W., Rose, J. W., Phillips, D. R.,

Nannizzi, L., Arfsten, A., Campbell, A. M., and Charo, I. F., *J. Biol. Chem.*

30 268, 1066, 1993.

- Dennis, M. S.; Henzel, W. J.; Pitti, R. M.; T., L. M.; Napier, M. A.; Deisher, T. A.; Bunting, S.; Lazarus, R., Platelet Glycoprotein IIb-IIIa Protein Antagonists from Snake Venoms: Evidence for a Family of Platelet-Aggregation Inhibitors, *Proc. Natl. Acad. Sci. USA*, 87, 2471, 1989.
- 5 Barker, P. L.; Bullens, S.; Bunting, S.; Burdick, D. J.; Chan, K. S.; Deisher, T.; Eigenbrot, C.; Gadek, T. R.; Gantzos, R.; Lipari, M. T.; Muir, C. D.; Napier, M. A.; Pitti, R. M.; Padua, A.; Quan, C.; Stanley, M.; Struble, M.; Tom, J. Y. K.; Burnier, J., P., Cyclic RGD Peptide Analogues as Antiplatelet Antithrombotics, *J. Med. Chem.*, 35, 2040, 1992.
- 10 McDowell, R. S.; Gadek, T. R., Structural Studies of Potent Constrained RGD Peptides, *J. Amer. Chem. Soc.*, 114, 9245, 1992.

**Glaxo**

- EP 537980, Oct. 13, 1992, B. Porter, et al.: Describes six cis-4-[4-(4-amidinophenyl)-1-piperazinyl]-1-hydroxycyclohexaneacetic acid analogs.
- 15 EO 0542363, Nov. 10, 1992, Porter, B., et al.: Describes 4-[4-amidinophenyl-piperazinyl]-piperidine-1-acetic acid analogs.
- WO 93/22303, Jan. 11, 1993, Middlemiss, D., et al.: Describes amidinophenyl-arylpiperazineacetic acid analogs.
- 20 WO 93/22303, Jan. 11, 1993, Middlemiss, D., et al.: Describes amidinophenyl-arylpiperazineacetic acid analogs.
- WO 93/14077, Jan. 15, 1993, B. Porter, et al.: Describes amidinophenyl-piperizinyll-piperidine-acetic acid analogs.
- EP 609282 A1, Aug. 10, 1994, Porter, B. et al.: Describes cyclohexane acetic acid derivatives.
- 25 EP 612313, Aug. 31, 1994, Porter, B., et al. Describes alpha-alkylpiperidineacetic acid derivatives.
- EP 93911769, Apr. 20, 1994, Midlemiss, D., et al.
- EP 637304 A1, Feb. 8, 1995, Middlemiss, D., et al. Piperazine Acetic acid
- 30 Derivatives.

- Hann, M. M.; Carter, B.; Kitchin, J.; Ward, P.; Pipe, A.; Broomhead, J.; Hornby, E.;  
Forster, M.; Perry, C., An Investigation of the Bioactive Conformation of  
ARG-GLY-ASP Containing Cyclic Peptides and Snake Venom Peptides  
Which Inhibit Human Platelet Aggregation, In *Molecular Recognition:*  
5 *Chemical and Biochemical Problems II*", S. M. Roberts, Ed., The Royal  
Society of Chemistry, Cambridge, 1992.
- Ross, B. C. Nonpeptide Fibrinogen Receptor Antagonists", (SAR leading to the  
discovery of GR 144053), In Seventh RSC-SCI Medicinal Chemistry  
Symposium, The Royal Society of Chemistry Fine Chemicals and  
10 Medicinals Group and SCI Fine Chemicals Group, Churchill College,  
Cambridge, 1993, L20.
- Pike, N. B.; Foster, M. R.; Hornby, E. J.; Lumley, P., Effect of the Fibrinogen  
Receptor Antagonist GR144053 Upon Platelet Aggregation *Ex Vivo*  
Following Intravenous and Oral Administration to the Marmoset and  
15 Cynomologous Monkey, *Thromb. Haem.* , 69, 1071, 1993.

**Hoechst**

- DE 4009506, Mar. 24, 1990, Konig, W., et al.: Describes Hydantoin-(Arg-Gly)-  
Asp-X analogs.  
20

**Hoffmann-La Roche**

- AU 9344935, (Der 94-118783/15), Mar. 10, 1994, : Describes Cyclic RGD analogs.  
EP 0592791, Apr. 20, 1994, Bannwarth, W. et al.: Describes Cyclic RGD analogs.

25 **Kogyo Gijutsuin**

- JP 06179696, June 28, 1994, Maruyama, S., et al.: Describes Gly-Pro-Arg-Pro-Pro  
and analogs.

**Kyowa Hakko Kogyo KK**

- 30 JP 05078244-A, Mar. 30, 1993: Describes dibenzo(b,e)oxepine derivatives.

**Laboratoire Chauvin**

WO 9401456, Jan. 20, 1994, Regnouf, D. V. J. et al.: Describes Ac-Arg-Gly-Asp-NHBn analogs.

5

**La Jolla Cancer Res. Fndn**

WO 9500544, Jan. 5, 1994, Pierschbacher, M. D. et al.

US 079441, Jan 5, 1994, Pierschbacher, M. D. et al.: Describes RGD Peptides.

10 **Lilly / COR**

EP 0635492, Jan. 25, 1995, Fisher, M. J., Happ, A. M., Jakubowski, J. A., Kinnick, M. D., Kline, A. D., Morin, Jr., J. M., Sall, M. A., Vasileff, R. T.: Describes compounds with 6,6-templates.

15 **Medical University of South Carolina**

EP 587770, Mar. 23, 1994 Halushka, P. V., Spicer, K. M.

**Merck**

EP 0368486 (Der 90-149427/20), Nov. 10, 1988: Describes X-R-Tyr-D-Y analogs.

20 

EP 0382451 (Der 90248531): Describes RGD-containing snake venom inhibitors.

EP 0382538 (Der 90248420): Describes RGD-containing snake venom inhibitors.

EP 0410537, July 23, 1990, R. F. Nutt, et al.: Describes cyclic RGD-containing peptides.

EP 0410539, July 25, 1990, R. F. Nutt, et al.: Describes cyclic RGD-containing

25 

peptides.

EP 0410540, July 25, 1990, R. F. Nutt, et al.: Describes cyclic RGD-containing peptides.

EP 0410541, July 25, 1990, R. F. Nutt, et al.: Describes cyclic RGD-containing peptides.

30 

EP 0410767, July 26, 1990, R. F. Nutt, et al.: Describes linear RGD-containing peptides.

- EP 0411833, July 26, 1990, R. F. Nutt, et al.: Describes cyclic RGD-containing peptides.
- EP 0422937, Oct. 11, 1990, R. F. Nutt, et al.: Describes cyclic RGD-containing peptides.
- 5 EP 0422938, Oct. 11, 1990, R. F. Nutt, et al.: Describes cyclic RGD-containing peptides.
- EP 0487238, October 13, 1991, T. M. Connolly, et al.: Describes Linear RGD-containing.
- EP 0437367 (Der 91209968), M. Sato et al.: Describes cyclic RGD-containing peptides, as inhibitors of osteoclast-mediated bone resorption.
- 10 EP 576898, Jan. 5, 1994, Jonczyk, A., et al.: Describes linear RGD peptide analogs for use in inhibition of cell adhesion.
- WO 9409029, Apr. 28, 1994, Nutt, R. F. and Veber, D. F., describes piperidinyethylpyrrolidinylacetyl-Asp-Trp(tetrazoles).
- 15 EP 618225, (Der 94-304404/38) Oct. 5, 1994, Describes RGD peptide analogs as antimetastatic compounds.
- DE 4310643, (Der 94-311172/39), Oct. 6, 1994, Jonczyk, A., et al.: Describes cyclic RGD analogs as antimetastatic agents.
- NO 9404093, Oct. 27, 1994, Jonczyk, A., et al.
- 20 EP 0632053, Jan. 4, 1995, Jonczyk, A., et al.: Describes cyclic RGD analogs as antimetastatic agents.
- EP 0479481, Sept. 25, 1991, M. E. Duggan et al.: Describes X-GlyAsp-Y linear semipeptides.
- EP 0478328, Sept. 26, 1991, M. S. Egbertson, et al.: Describes tyrosine derivatives.
- 25 EP 0478362, Sept. 27, 1991 M. E. Duggan et al. : Describes X-Gly-(3-phenethyl) $\beta$ Ala analogs.
- EP 0478363, Sept. 27, 1991, W. L. Laswell, et al.: Describes Tyrosine sulfonamides.
- EP 0512829, May, 7, 1992, Duggan, M. E., et al.: Describes chiral 3-hydroxy-6-(4-piperidiny)heptanoyl- $\beta$ -X- $\beta$ -Ala-OH analogs, with variations on X and the
- 30 central alkanoyl chain.

- EP 0512831, May, 7, 1992, Duggan, M. E., et al.: Describes chiral 2-oxo-3-(Piperidinylethyl)piperidinylacetyl- $\beta$ -X- $\beta$ -Ala-OH analogs, with variations on X and the central piperidinyl ring.
- 5 EP 0528586, August 5, 1992, M. S. Egbertson, et al.: Describes tyrosine sulfonamides as inhibitors of osteoclast-mediated bone resorption.
- EP 0528587, August 5, 1992, M. S. Egbertson, et al.: Describes tyrosine sulfonamides as inhibitors of osteoclast-mediated bone resorption.
- EP 0540334, October 29, 1992, G. D. Hartman, et al.: Describes benzimidazoles.
- 10 US 5227490, Feb. 21, 1992, G. D. Hartman, et al.: Describes Tyrosine sulfonamides.
- CA 2088518, Feb. 10, 1993, Egbertson, M. S., et al.: Describes aminoalkyl-phenyl derivs. as bone resorption inhibits.
- US 5206373-A, (Der 93-151790/18) Apr. 27, 1993, Chung, J. Y. L., et al.: Describes MK-383-type compounds.
- 15 WO 9316994, (Der 93-288324/36), Sep. 2, 1993, Chung, J. Y. L., et al.: Describes pyridinylbutyl-L-Tyrbutylsulfonamide.
- US 5264420-A, Nov. 23, 1993, Describes piperidinylalkyl-Gly-betaAla analogs.
- US 5272158, Dec. 21, 1993, Hartman, G. D. et al.: Describes piperidinylethylisoinole analogs.
- 20 US 5281585, Jan. 25, 1994, Ihle, N., et al.: Describes 3-(piperidinylethyl)-piperidinone analogs.
- GB 945317 A, Mar. 17, 1994 (Priority US 34042A, Mar. 22, 1993).
- GB 2271567 A, Apr. 20, 1994, Hartman, G. D. et al.: Describes compounds replacing Tyr with beta-phenylsuccinate.
- 25 US 5294616, (Der 94-091561/11) Mar. 15, 1994, Egbertson, M. S., et al.
- US 5292756, (Der 94-082364) Apr. 8, 1994, Hartman, G. D. et al.
- WO 9408577, Apr. 28, 1994, Hartman, G. D., et al.
- WO 9408962, Apr. 28, 1994, Hartman, G. D., et al.
- WO 9409029, (Der 94-151241/18) Apr. 28, 1994, Hartman, G. D., et al. Describes
- 30 piperidinylpyrrolinylacetyl-Asp-Trp-tetrazoles.
- US 5312923, May 17, 1994, Chung, J. Y. L. et al.

- HU 9400249, May 30, 1994, Gante, J. et al.: Describes piperazine analogs.
- WO 9412181, (Der 94-199942/24), Jun. 9, 1994, Egbertson, M. S. et al.: Describes  
piperidinylethyloxyphenyl acetic acid analogs
- US 5321034, June 14, 1994, Duggan, M. E., et al.: Describes Piperidinylalkyl-  
5        betaamino acids.
- US 5334596, Aug. 2, 1994, Hartman, G. D. et al.
- EP 0608759 A, Aug. 3, 1994, GAnte, J. P. et al.: Describes amidinopiperazinyl  
compounds.
- WO 9418981, (Der 94-293975/36) Sep. 1, 1994, Claremon, D. A.. et al.: Describes  
10        Many different amine surrogate.
- GB 2276384, (Der 94-287743/36) Sep. 28, 1994, Claremon, D. A., Liverton, N.,:  
Describes piperidinylethylquinazoline analogs.
- WO 9422825, Oct. 13, 1994, Claremon, D. A.. Liverton, N. J.,: Describes  
piperidinylethyl-retro-benzodiazepine analogs.
- 15    EP 0623615A, Nov. 9, 1994, Raddatz, P. et al: Describes  
amidinophenyloxazolidinylmethyl-piperidine-4-carboxylic acid and analogs.
- WO 9504531, Feb. 16, 1995, Hartman, G D., et al.: Describes  
piperidinylalkylheterocycles.
- Nutt, R. F.; Brady, S. F.; Colton, C. D.; Sisko, J. T.; Ciccarone, T. M.; Levy, M. R.;  
20        Duggan, M. E.; Imagine, I. S.; Gould, R. J.; Anderson, P. S.; Veber, D. F.,  
Development of Novel, Highly Selective Fibrinogen Receptor Antagonists as  
Potentially Useful Antithrombotic Agents, In *Peptides, Chemistry and  
Biology, Proc. 12th Amer. Peptide Symp.*, J. A. Smith and J. E. Rivier, Ed.,  
ESCOM, Leiden, 1992; 914.
- 25    Hartman, G. D.; Egbertson, M. S.; Halszenko, W.; Laswell, W. L.; Duggan, M. E.;  
Smith, R. L.; Naylor, A. M.; Manno, P. D.; Lynch, R. J.; Zhang, G.; Chang,  
C. T. C.; Gould, R. J., Non-peptide Fibrinogen Receptor Antagonists. 1.  
Discovery and Design of Exosite Inhibitors, *J. Med. Chem.* , 35, 4640, 1992.
- Gould, R. J.; Barrett, S.; Ellis, J. D.; Holahan, M. A.; Stranieri, M. T.; Theoharides,  
30        A. D.; Lynch, J. J.; Friedman, P. A.; Duggan, M. E.; Ihle, N. C.; Anderson,  
P. S.; Hartman, G. D., Characterization of L-703,014, A Novel Fibrinogen

Receptor Antagonist, Following Oral Administration to Dogs, *Thromb. Haem.*, 69, 539, 1993.

**Merrell Dow**

- 5 WO 93/24520, May 14, 1993, Harbeson, S. L., et al.: Describes cyclic RGD peptides.
- WO 9324520, Dec. 9, 1993, Harbeson, Bitonti, J., A.: Describes cyclic RGD analogs as antimetastatic agents.
- WO 9429349, Dec. 22, 1994, Harbeson, Bitonti, J., A.: Describes cyclic RGD
- 10 analogs as antimetastatic agents.

**Nippon Steel Corp**

- WO 9405696, Mar. 17, 1993, Sato, Y., et al.,
- EP 628571, Dec. 14, 1994, Sato, Y. et al.
- 15 WO 9501371, Jan. 12, 1995, Sato, Y. et al.: Describes RWSRGDW analogs.

**ONO Pharmaceuticals**

- JP 05286922 (Der 93-383035/48), Describes guanidinophenol alkylbenzoic acid esters.
- 20

**Roche**

- EP 038,362, Feb. 19, 1990, M. Muller, et al.: Describes X-NHCHYCO-Gly-Asp-NHCHZCO<sub>2</sub>H analogs.
- EP 0372486, June, 13, 1990, Allig, L., et al.
- 25 EP 0381033, July, 8, 1990, Allig, L., et al.
- EP 0384362, August 29, 1990, Allig, L. et al.: Describes amidinophenyl-linked Gly-Asp-X semipeptides.
- EP 0445796, Sept. 11, 1991, Allig, L. et al.: Describes amidinophenyl-linked Gly-Asp-X semipeptides.



- EP 0505868, Sept. 30, 1992, Allig, L. et al.: Describes N-acyl-alphaamino acid derivatives, ie. analogs from EP0381003 with variations in the phenyloxyacetic acid group.
- US 5273982-A, (Der 94-006713/01) Dec. 28, 1993: Describes amidinophenyl-linked Gly-Asp-X semipeptides.
- 5 Alig, L.; Edenhofer, A.; Hadvary, P.; Hurzeler, M.; Knopp, D.; Muller, M.; Steiner, B.; Trzeciak, A.; Weller, T., Low Molecular Weight, Non-peptide Fibrinogen Receptor Antagonists, *J. Med. Chem.*, 35, 4393, 1992.
- 10 **Rhone-Poulenc Rorer**
- US 4952562, Sept. 29, 1989, S. I. Klein et al.: Describes X-Gly-Asp-Val-OH analogs.
- US 5064814, (Der 91-353169/48) Apr. 5, 1990: Describes Piperidinyl-azetidiny-Asp-X analogs.
- 15 WO 9104746, Sept. 25, 1990, S. I. Klein et al.: Describes X-Asp-Val-OH analogs.
- WO 91/05562, Oct. 10, 1989, S. I. Klein et al.: Describes X-Gly-Asp-Val-OH analogs.
- WO 91/07976, (Der 91-192965) Nov. 28, 1990, S. I. Klein et al.: Describes X-cycloAA-Asp-Val-OH analogs.
- 20 WO 91/04746, S. I. Klein et al.: Describes des-AminoArginine RGD analogs.
- WO 92/18117, Apr. 11, 1991, S. I. Klein et al.: Describes X-Asp-Val-OH analogs.
- US 5086069, (Der 92-064426/08) Apr. 2, 1992, : Describes X-Gly-Asp-Val-OH analogs.
- WO 92/17196, Mar. 30, 1992, S. I. Klein et al.: Describes X-Gly-Asp-Val-OH
- 25 analogs.
- US 5328900, (Der 94-221950/27) Jul. 12, 1992, : Describes X-azetidiny-Asp-Val-OH analogs.
- US 5332726, (Der 94-241043/29) Jul. 26, 1994, : Describes guanidinoalkanoyl-(N-alkyl)Gly-Asp-Val-OH analogs.
- 30 WO 93/11759, Dec. 7, 1992, S. I. Klein et al.: Describes Bis-guanidinoaklanoic acid analogs.

EP 0577775, Jan 12, 1994, Klein, S. I. et al.  
CA 2107088, Sept. 29, 1992, Klein, S.I. et al.

**Sandoz**

- 5 EP 0560730, Mar. 8, 1993 G. Kottirisch and R. Metternich: Describes amidinophenylalkanamid-S- $\alpha$ -acetic acid analogs.  
G. Kottirisch, et al. Biorg. Med. Chem. Lett 3, 1675-1680, 1993, Describes amidinophenylacetyl-(Gly-Asp- $\gamma$ -lactam mimetic)analogs.

10 **Schering AG**

E 530937, Mar. 10, 1993, Noeski-Jungblut, C., et al. "Collagen Induced Platelet Aggregation Inhibitor."

**Searle / Monsanto**

- 15 EP 0319506, (Der 89-3195506) Dec. 2, 1988, S. P. Adams, et al.: Describes RGD-X analogs.  
EP 0462,960, June, 19.1991, Tjoeng, F. S., et al.: Describes guanidinoctanoyl-Asp-Phe analogs.  
US 4857508, S. P. Adams, et al.: Describes RGD analogs.
- 20 EP 0502536, (Der 92-301855) Mar. 3, 1991, R. B. Garland, et al.: Describes amidinophenylalkanoyl-Asp-Phe analogs.  
EP 0319506, Dec. 2, 1988, S. P. Adams et al.: Describes RGD<sub>X</sub> analogs.  
US 4992463, Aug. 18, 1989: Describes guanidinoalkanoyl-Asp-X analogs.  
US 5037808, Apr. 23, 1990: Describes guanidinoalkanoyl-Asp-X analogs.
- 25 EP 0454651 A2, Oct. 30, 1991, Tjoeng, F. S., et al.: Describes amidinoalkanoyl-Asp-X analogs.  
US 4879313, July, 20, 1988: Describes guanidinoalkanoyl-Asp-X analogs.  
WO 93/12074, Nov. 19, 1991, N. Abood, et al.: Describes amidinophenylalkanoyl- $\beta$ -X-AlaOH analogs.

- WO 93/12103, Dec. 11, 1991, P. R. Bovy, et al.: Describes amidinophenylalkanoyl- $\beta$ -X-lactone analogs.
- US 5091396, Feb. 25, 1992, Tjoeng, F. S., et al.: Describes amidinoalkanoyl-Asp-X analogs.
- 5 WO 92/15607, Mar. 5, 1992, Garland, R. B., et al.: Describes amidinophenylalkanoyl-Asp-X analogs.
- WO 93/07867, Apr. 29, 1993, P. R. Bovy, et al.: Describes amidinophenylamidopropionyl- $\beta$ -X-AlaOH analogs.
- US 888686, May 22, 1992, Bovy, P. R. et al.
- 10 CA 2099994, Sept. 7, 1992, Garland, R. B., et al.
- US 5254573, Oct. 6, 1992, Bovy, P. R., et al.: Describes amidinophenylamidopropionyl- $\beta$ -X- $\beta$ -Ala-OH.
- (PF54C06), EP 0539343, Oct. 14, 1992, P.R. Bovy et al.: Describes amidinophenylamidopropionyl- $\beta$ -X- $\beta$ -Ala-OH.
- 15 WO 93/12074, Nov. 27, 1992, N. A. Abood, et al.: Describes amidinophenylalkylamido-(R)-Asp-(i.e. retro-Asp)-alkyl and aryl amides and sulfonamides.
- WO 93/12103, Dec. 11, 1992, P. R. Bovy et al.: Describes amidinophenylalkanoyl-Asp-X lactones
- 20 EP 0 539343, Apr. 28, 1993, Bovy, P. R., et al.
- EP 0542708, May, 19, 1993, Bovy, P. R., et al.
- WO 94/00424, June 23, 1993, Abood, N. A., et al.: Describes amidinophenylalkanoic acid lactones related to previous compounds.
- WO 93/16038, Aug. 16, 1993, Miyano, M. et al.: Describes amidinophenylpentanoyl- $\beta$ -arylsulfonamidomethyl- $\beta$ -Ala-OH analogs.
- 25 WO 93US7975, Aug. 17, 1993, Zablocki, J. A., Tjoeng, F. S.
- WO 93/18058, Sept. 16, 1993, Bovy, P. R. et al.: Describes amidinophenylamidoproionoyl-Asp-X-OH analogs.
- US 5254573, Oct. 19, 1993, Bovy, P. R., et al., Describes amidinophenylpropionyl-amino acid dervs.
- 30

- US, 5272162, Dec. 21, 1993, Tjoeng, F. S., et al.: Describes amidinophenyl-X-NHCO- $\beta$ -Y- $\beta$ -Ala-OH analogs.
- EP 0574545, Dec. 22, 1993, Garland, R. B., et al.: AmidinophenylX-Asp Analogs.
- WO 9401396, Jan. 20, 1994, Tjoeng, F. S., et al., Describes
- 5 amidinophenylalkylamido-amino acid derivatives.
- WO 9405694, (Der 94-101119/12) Mar. 17, 1994, Zablocki, et al.: Describes amidinophenylalkylamido-amino acid derivatives.
- US 5314902, May 24, 1994, Adams, S. P. et al.: Describes amidinophenylamidoalkanoyl derivatives.
- 10 WO 9418162, Aug. 18, 1994, Adams, S. P., et al.: Describes amidinophenylalkanoyl-amino acid derivatives.
- WO 9419341, Sept. 1, 1994, Tjoeng, F. S., et al.: Describes amidinophenylnipecotic acid derivatives.
- US 5344837, (Der 94-285503/35), Sept. 6, 1994, Zablocki, J. A., et al.
- 15 EP 614360, Sept. 14, 1994, Bovy, P. R., et al.
- WO 9420457, (Der 94-302907/37) Sep. 15, 1994, Tjoeng, F. S. et al.
- Amidinophenyl compounds with central ring.
- WO 9421602, (Der 94-316876/39), Sept. 29, 1994, Tjoeng, F. S., et al. Describes guanidinoalkylaminocarbonylaminoacid derivatives.
- 20 WO 9422820, Oct. 13, 1994, Abood, N. A., et al.: Describes amidinophenylpyrrolidinonyl- $\beta$ -Ala derivatives.
- EP 630366, Dec. 28, 1994, Bovy, P. R., et al.
- US 5378727, Jan. 3, 1995, Bovy, P. R. et al.
- K. F. Fok, et al., Int. J. Peptide Prot. Res., 38, 124-130, 1991, SAR of RGDY
- 25 analogs.
- J. A. Zablocki, et al. J. Med. Chem. 35, 4914-4917, 1992, SAR summary of guanidinoalkanoyl-Asp-Phe analogs.
- Tjoeng, F. S.; Fok, K. F.; Zupec, M. E.; Garland, R. B.; Miyano, M.; Panzer-Knodle, S.; King, L. W.; Taite, B. B.; Nicholson, N. S.; Feigen, L. P.; Adams, S. P.,
- 30 Peptide Mimetics of the RGD Sequence, In *Peptides, Chem. and Biol. Proc.*

*12th Amer. Peptide Symp.*, J. A. Smith and J. E. Rivier, Ed., ESCOM, Leiden, 1992; 752.

- Nicholson, N.; Taite, B.; Panzer-Knodle, S.; Salyers, A.; Haas, N.; Szalony, J.; Zablocki, J.; Feigen, L.; Glenn, K.; Keller, B.; Broschat, K.; Herin, M.;  
5 Jacqmin, P.; lesne, M., An Orally Active Glycoprotein IIb/IIIa Antagonist - SC-54684, *Thromb. Haem.*, 69, 975, 1993.

**SmithKline Beecham Corporation**

- WO 93/00095, WO 94/14776, and WO 95/18619, Bondinell, et al., Describes (6,7)  
10 bicyclic fibrinogen templates.  
WO 94/12478, Keenan, et al., , Describes (6,5) bicyclic fibrinogen templates.  
WO 94/22440, Callahan, et al., Describes (8,6) bicyclic fibrinogen templates.  
WO 94/22444, Callahan, et al., Describes (8,6,7) tricyclic fibrinogen templates.  
WO 94/29273, Samanen, J., Describes (6,6) bicyclic fibrinogen templates.

15

**Sumitomo Pharm. Co. Ltd.**

WO 9501336, June 6, 1994, Ikeda, Y., et al., Describes piperidinyloxyacetyl-Tyr-piperidinyloxyacetic acid derivatives.

20 **Sumitomo Seiyaku KK**

JP 06025290, (Der 94-077374/10) Feb. 1, 1994. Describes multimeric RGDT.

**Taisho Pharm. (Teijin, Ltd)**

- JP 05230009, (Der 93-317431/40, Feb. 24, 1992: Describes amidino-Cbz-meta-  
25 aminophenylpropionate.  
JP 9235479, Feb. 24, 1992: Describes Amidinophenylcarbarnates.  
(PFD4C06), WO 94/17804, Aug. 18, 1994, Mizushima, Y. Pharm. Comp for  
Treating Cerebral Thrombosis.  
(EP 634171), Jan. 18, 1995, Nizushima, M. Pharm. Comp for Treating Cerebral  
30 Thrombosis. Prostaglandins

**Takeda**

- EP 0529858, Apr. 3, 1993, H. Sugihara, et al.: Describes amidinobenzoyl-Gly-Piperazinone analogs.
- EP 606881, Jul. 20, 1994, Cyclic peptides with beta and gamma turns.
- 5 EP 614664, Sept. 14, 1994, Miyake, A., et al: Quinolonecarboxylic Acids as cell adhesion inhibitors.

**Tanabe**

- WO 89/07609, T. J. Lobl, et al.: Describes RGD analogs.
- 10 WO 92/00995, July 9, 1991, T. J. Lobl, et al.: Describes cyclic RGD analogs.
- WO 93/08823, Nov. 6, 1991, T. C. McKenzie: Describes guanidinoalkanoyl-Gly-Asp-X analogs.
- CA 2087021, Jan 10, 1991, Lobl, T. J., et al: Describes cyclic RGD analogs.
- WO 92/08464, Nov. 15, 1991, T. C. McKenzie, et al.: Describes.

15

**Telios / La Jolla Cancer Research**

- US. 4578079, Nov. 22, 1983, E. Ruoslahti, and M. Pierschbacher: Describes X-RGD-Y analogs.
- US. 4614517, June 17, 1985, E. Ruoslahti, and M. Pierschbacher: Describes X-
- 20 RGD-Y analogs.
- US. 4792,525, June 17, 1985, E. Ruoslahti, and M. Pierschbacher: Describes X-RGD-Y analogs.
- US 4879237, (Der 90-154405/20) May, 24, 1985, Describes X-RGD-Y analogs.
- WO 91/15515, (Der 91-325173/44) Apr. 6, 1990, describes cyclic RGD analogs.
- 25 US. 5041380, 1991, E. Ruoslahti, and M. Pierschbacher: Describes RGD-X analogs.
- WO 95/00544 Jan. 5, 1995, Craig, W. S., et. al.
- Cheng, S.; Craig, W. S.; Mullen, D.; Tschopp, J. F.; Dixon, D.; Pierschbacher, M. F., Design and Synthesis of Novel Cyclic RGD-Containing Peptides as Highly Potent and Selective Integrin  $\alpha_{IIb}\beta_3$  Antagonists, *J. Medicin. Chem.* ,
- 30 37, 1, 1994.

Collen, D.; Lu, H. R.; Stassen, J.-M.; Vreys, I.; Yasuda, T.; Bunting, S.; Gold, H. K.,  
Antithrombotic Effects and Bleeding Time Prolongation with Synthetic  
Platelet GPIIb/IIIa Inhibitors in Animal Models of Platelet-Mediated  
Thrombosis, *Thrombosis and Haemostasis*, 71, 95, 1994.

5

**Temple U.**

WO 9409036, (Der 94-151248/18), Apr. 28, 1994, Describes disintegrin peptides.

**Terumo KK**

- 10 JP 6279389, Oct. 4, 1994, Obama, H., et al.: Describes 3-(4-  
amidinophenyloxymethyl)phenylamidopropionic acid analogs (ala Roche I-  
35).

**Karl Thomae / Boehringer Ingelheim**

- 15 EP 0483667, May 6, 1992, Himmelsbach, F., et al.: Describes amidinobiphenyl-  
oxymethyl-2-pyrrolidinone-acetic acid.  
EP 0496378, Jan. 22, 1992, Himmelsbach, F., et al.: Describes amidinobiphenyl-  
aminocarbonylcyclohexylcarboxylic acid analogs.  
EP 0503548, Sep. 16, 1992, Himmelsbach, F., et al.: Describes amidinophenyl-  
20 pyrrolidinone-phenylpropionic acid analogs.  
AU A-86926/91, May 7, 1992, Himmelsbach, F. et al.: Describes amidinophenyl  
compounds.  
EP 0528369, Feb. 24, 1993, Austel, V., et al.: Describes amidinobiphenyl-  
oxymethyl-2-pyrrolidinone-acetic acid.  
25 EP 0537696, Apr. 21, 1993 Linz, G., et al.: Describes amidinophenyl-pyridazine  
analog.  
DE 4124942, Jan. 28, 1993, Himmelsbach, F. et al.: Describes amidino-  
triarylproionic acid analogs.  
DE 4129603, Mar. 11, 1993, Pieper, H, et al.: Describes amidinobiphenyl-  
30 benzimidazole.

- EP 0547517 A1, (Der 93-198544) June 23, 1993, Soyka, R., et al.: Describes pyridyl compounds.
- EP 0567966, Nov. 3, 1993, Himmelsbach, F., et al.: Describes amidinobiphenyl-oxymethyl-2-pyrrolidinone-acetic acid.
- 5 EP 0567967, Nov. 3 1993, Weisenberger, J., et al.: Describes amidinobiphenyl-oxymethyl-2-pyrrolidinone-acetic acid.
- EP 0567968, Nov. 3, 1993, Linz, G., et al.: Describes amidinobiphenyl-lactam-acetic acid and amidinophenyllactamphenylpropionic acid analogs.
- EP 0574808, June 11, 1993, Pieper, H., et al.: Describes amidinobiphenyl-X-acetic acid ester analogs.
- 10 Der 93-406657/51, Austel, V., et al.: Describes amidinobiphenyl analogs.
- EP 587134, (Der 94-085077/11) Mar. 16, 1994, Himmerlsbach, F. D. D., et al., Describes amidinophenyltriazolone analogs.
- EP 589874, Apr. 6, 1994, Grell, W., et al.
- 15 (P534005), DE 4234295, Apr. 14, 1994, Pieper, H., et al., Describes heteroaryl-azacyclohexylcarboxylic acid analogs.
- EP 0592949, Apr. 20, 1994, Pieper, H. D., et al., Describes amidinophenyl-4piperidinamido-4-cyclohexylcarboxylic acid analogs.
- EP 596326, May, 11, 1994, Maier, R. et al.
- 20 DE 4241632, June 15, 1994, Himmelsbach, F., et al., Describes piperidinophenylamido-phenylpropionyl analogs.
- EP 0604800 A, Jul. 6, 1994, Himmelsbach, F. et al., Describes piperidinophenylamido-phenylalanine derivatives.
- DE 4302051, (Der 94-235999/29) July, 28, 1994, describes compounds containing a 2H-pyrazol-5-one.
- 25 EP 0608858 A, Aug. 3, 1994, Linz, G. D., et al., Describes amidino-biphenyl compounds.
- DE 4304650, (Der 94-256165/32), Aug. 18, 1994, Austel, V., et al., describes compounds with a 5,6 template.
- 30 EP 611660, Aug, 24, 1994, Austel, V., et al., Describes tricyclic template.



- DE 4305388, (Der 94-264904/33), Aug. 25, 1994, Himmelsbach, F., et al.,  
Describes 6,6 and 7,6 templates.  
(P5D4005), EP 612741, (Der 94-265886/33), Aug. 31, 1994, Himmelsbach, F., et  
al., Describes 6,6 and 7,6 templates.
- 5 EP 0639575 A, Feb. 22, 1995, Linz, G., et al.: Describes tetrahydrothiazolo-  
[5,4,c]pyridine cation replacements.  
DE 4324580, Jan. 26, 1995, Linz, G. et al.  
EP 0638553, Feb. 15, 1995, Himmelsbach, F., et al.  
F. Himmelsbach, V. Austel, G. Kruger, H. Pieper, H. Weisenberger, T. H. Muller,  
10 and W. G. Eisert, in XIIth Int. Symp. on Med. Chem. Basel, Book of  
Abstracts, 47, 1992.  
V. Austel, W. Eisert, F. Himmelsbach, G. Kruger, G. Linz, T. Muller, H. Pieper, and  
J. Weisenberger, Natl. Mtg. Amer. Chem. Soc. Book of Abstracts, Denver,  
Div. Med. Chem., 1993.
- 15 Muller, T. H.; Schurer, H.; Waldmann, L.; Bauer, E.; Himmelsbach, F.; Binder, K.,  
Orally Activity of BIBU 104, a Prodrug of the Non-peptide Fibrinogen  
Receptor Antagonist BIBU 52, in Mice and Monkeys, *Thromb. Haem.*, 69,  
975, 1993.
- 20 **Univ. California**  
WO 94/14848, July, 7, 1994, Zanetti, M. RGD peptides from CDR.
- Univ. New York**  
WO 94/00144, June 29, 1993, Ojima, I. et al.: Describes RGD peptide multimers.
- 25 **Yeda Res. and Dev. Co.**  
WO 93/09795, (Der 93-182236/22), Lido, O. et al.: Describes Guanidinopentanoic  
acid analogs.
- 30 **Zeneca**

WO 9422834, Oct. 13, 1994, Wayne, M. G., et al. Describes pyridinopiperazino-phenylcarbonyl-amino acids.

WO 9422835, Oct. 13, 1994, Wayne, M. G., et al. Describes pyridinopiperidino-amidophenylacetic acids.

5 EP 632016, Jan. 4, 1995, Brewster, A. G., et al. Describes pyridinopropionylhydrazinylbenzoyl analogs.

EO 632019, Jan. 4, 1995, Brown, G., Shute, R. E.

EO 632020, Jan. 4, 1995, Brown, G., Shute, R. E.

10 In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. The meaning of  
15 any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical

20 Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

C<sub>1-4</sub>alkyl as applied herein means an optionally substituted alkyl group of 1 to 4 carbon atoms, and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. C<sub>1-6</sub>alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C<sub>0-4</sub>alkyl and C<sub>0-6</sub>alkyl

25 additionally indicates that no alkyl group need be present (e.g., that a covalent bond is present).

Any C<sub>1-4</sub>alkyl or C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl or C<sub>1-6</sub>oxoalkyl may be optionally substituted with the group R<sup>x</sup>, which may be on any carbon atom that results in a stable structure and is available by conventional synthetic techniques.

30 Suitable groups for R<sup>x</sup> are C<sub>1-4</sub>alkyl, OR', SR', C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylsulfonyl,

C<sub>1-4</sub>alkylsulfoxyl, -CN, N(R')<sub>2</sub>, CH<sub>2</sub>N(R')<sub>2</sub>, -NO<sub>2</sub>, -CF<sub>3</sub>, -CO<sub>2</sub>R', -CON(R')<sub>2</sub>, -COR',  
 -NR'C(O)R', OH, F, Cl, Br, I, N<sub>3</sub>, or CF<sub>3</sub>S(O)<sub>r</sub>-, wherein r is 0 to 2.

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or  
 naphthyl substituted by one to three substituents, such as those defined above for  
 5 alkyl, especially C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkthio, trifluoroalkyl, N<sub>3</sub>, OH, CO<sub>2</sub>H  
 F, Cl, Br or I.

Het, or heterocycle, indicates an optionally substituted five or six membered  
 monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three  
 heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable  
 10 and available by conventional chemical synthesis. Illustrative heterocycles are  
 benzofuran, benzimidazole, benzopyran, benzothiophene, biotin, furan, imidazole,  
 indoline, morpholine, piperidine, piperazine, pyrrole, pyrrolidine, pyridine,  
 tetrahydropyridine, pyridine, thiazole, thiophene, quinoline, isoquinoline, and tetra-  
 and perhydro- quinoline and isoquinoline. Any accessible combination of up to  
 15 three substituents on the Het ring, such as those defined above for alkyl that are  
 available by chemical synthesis and are stable are within the scope of this invention.

C<sub>3-7</sub>cycloalkyl refers to an optionally substituted carbocyclic system of three  
 to seven carbon atoms, which may contain up to two unsaturated carbon-carbon  
 bonds. Typical of C<sub>3-7</sub>cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl,  
 20 cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl. Any combination of up to  
 three substituents, such as those defined above for alkyl, on the cycloalkyl ring that  
 is available by conventional chemical synthesis and is stable, is within the scope of  
 this invention.

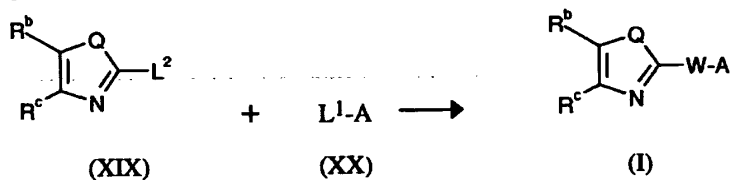
When R<sup>b</sup> and R<sup>c</sup> are joined together to form a five- or six-membered  
 25 aromatic or non-aromatic carbocyclic or heterocyclic ring fused to the ring to which  
 R<sup>b</sup> and R<sup>c</sup> are attached, the ring formed will generally be a five- or six-membered  
 heterocycle selected from those listed above for Het, or will be a phenyl, cyclohexyl  
 or cyclopentyl ring. Preferably R<sub>b</sub> and R<sub>c</sub> will be -D1=D2-D3=D4 wherein D1 - D4  
 are independently CH, N or C-R<sub>x</sub> with the proviso that no more than two of D1 - D4

are N. Most preferably, when R<sup>b</sup> and R<sup>c</sup> are joined together they form the group -CH=CH-CH=CH-.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, BrZ refers to the o-bromobenzyloxycarbonyl radical, ClZ refers to the o-chlorobenzyloxycarbonyl radical, Bzl refers to the benzyl radical, 4-MBzl refers to the 4-methyl benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to C<sub>1-4</sub>alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl. Tet refers to 5-tetrazolyl.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethyl amine, EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride. HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DME refers to dimethoxyethane, DMF refers to dimethylformamide, NBS refers to N-bromosuccinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to 1-propanephosphonic acid cyclic anhydride, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

Compounds of the formula (I)-(V) are prepared, for example, by reacting a compound of formula (XIX) with a compound of formula (XX), wherein L<sup>1</sup> and L<sup>2</sup> are groups which may react to form a covalent bond in the moiety W, by methods generally known in the art.



Typical methods include coupling to form amide bonds, nucleophilic displacement reactions and palladium catalyzed couplings. For instance, when W

contains an ether or amine linkage, the bond may be formed by a displacement reaction, and one of  $L^1$  and  $L^2$  will contain an amino or hydroxy group and the other will contain a displaceable group, such as a chloro, bromo or iodo group. When W contains an amide bond, typically one of  $L^1$  and  $L^2$  will contain an amino group, and  
 5 the other will contain a carboxylic acid group. In another approach,  $L^1$  may be an aryl or heteroaryl bromide, iodide or trifluoromethylsulfonyloxy derivative and  $L^2$  may contain an amino group and the amide linkage may be formed by palladium-catalyzed aminocarbonylation with carbon monoxide in a suitable solvent such as dimethylformamide or toluene.

10 It will be apparent that the precise identity of  $L^1$  and  $L^2$  will be dependent upon the site of the linkage being formed. General methods for preparing the linkage  $-(CHR'')_r-U-(CHR'')_s-V-$  are described, for example, in EP-A 0 372 486 and EP-A 0 381 033 and EP-A 0 478 363, which are incorporated herein by reference.

For instance, if V is CONH,  $L^1$  may be  $-NH_2$ ,  $L^2$  may be OH (as in an acid)  
 15 or Cl (as in an acid chloride), and  $R^{6''}$  may be  $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-C(O)$ , with any functional groups optionally protected. For example,  $R^{6''}$  may be (benzyloxycarbonyl-amidino)benzoyl- or  $(N^{\alpha}\text{-Boc}, N^{\text{guan}}\text{-Tos})\text{arginyll-}$ . When  $L^2$  is OH, a coupling agent is used.

Similarly, if V is NHCO,  $L^1$  may be  $-CO_2H$  or  $CO-Cl$ ,  $L^2$  may be  $-NH_2$ , and  
 20  $R^{6''}$  may be  $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-$ . For example,  $R^{6''}$  may be (benzyloxycarbonyl-amidino)phenyl, (benzyloxycarbonylamino)methylbenzyl- or 6-(benzyloxycarbonylamino)hexyl-.

Where V is  $NHSO_2$ ,  $L^1$  may be  $SO_2Cl$ ,  $L^2$  may be  $-NH_2$  and  $R^{6''}$  may be as above. Where V is  $SO_2NH$ ,  $L^1$  may be  $-NH_2$  and  $L^2$  may be  $SO_2Cl$ . Methods to  
 25 prepare such sulfonyl chlorides are disclosed, for instance, in *J. Org. Chem.*, 23, 1257 (1958).

If V is  $CH=CH$ ,  $L^1$  may be  $-CHO$ ,  $L^2$  may be  $CH=P-Ph_3$  and  $R^{6''}$  may be  $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-$ . Alternately,  $L^1$  may be  $CH=P-Ph_3$ ,  $L^2$  may be  $CHO$ , e.g.,  $R^{6''}$  may be  $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_{s-1}-CHO$ .

Where V is  $\text{CH}_2\text{CH}_2$  may be obtained by reduction of a suitably protected compound wherein V is  $\text{CH}=\text{CH}$ .

Where V is  $\text{CH}_2\text{O}$ ,  $\text{CH}_2\text{N}$  or  $\text{C}\equiv\text{C}$ ,  $\text{L}^1$  may be  $-\text{OH}$ ,  $-\text{NH}$  or  $-\text{C}\equiv\text{CH}$ , respectively;  $\text{L}^2$  may be  $-\text{Br}$ ; and  $\text{R}^{6''}$  may be

- 5  $\text{W}-(\text{CR}'_2)_q-\text{Z}-(\text{CR}'\text{R}^{10})_r-\text{U}-(\text{CR}'_2)_s$ . For example,  $\text{R}^{6''}$  may be (benzyloxycarbonylamino)-methylbenzyl- or 2-(N-benzyl-4-piperidinyl)-ethyl. Similarly where U or V is  $\text{OCH}_2$ ,  $\text{NR}'\text{CH}_2$  or  $\text{C}\equiv\text{C}$ ,  $\text{L}^1$  may be  $-\text{CH}_2\text{Br}$  and  $\text{L}^2$  may be  $-\text{OH}$ ,  $-\text{NH}$  or  $-\text{C}\equiv\text{CH}$ , respectively. Alternately, when U or V is  $\text{C}\equiv\text{C}$ ,  $\text{L}^1$  may be  $\text{Br}$ ,  $\text{I}$  or  $\text{CF}_3\text{SO}_3$ ,  $\text{L}^2$  may be  $\text{C}\equiv\text{CH}$  and the coupling may be catalyzed by
- 10 palladium and a base.

Compounds wherein V is  $\text{CHOHCH}_2$  may be prepared from a suitably protected compound where V is  $\text{CH}=\text{CH}$  by the procedure disclosed in *J. Org. Chem.*, 54, 1354 (1989).

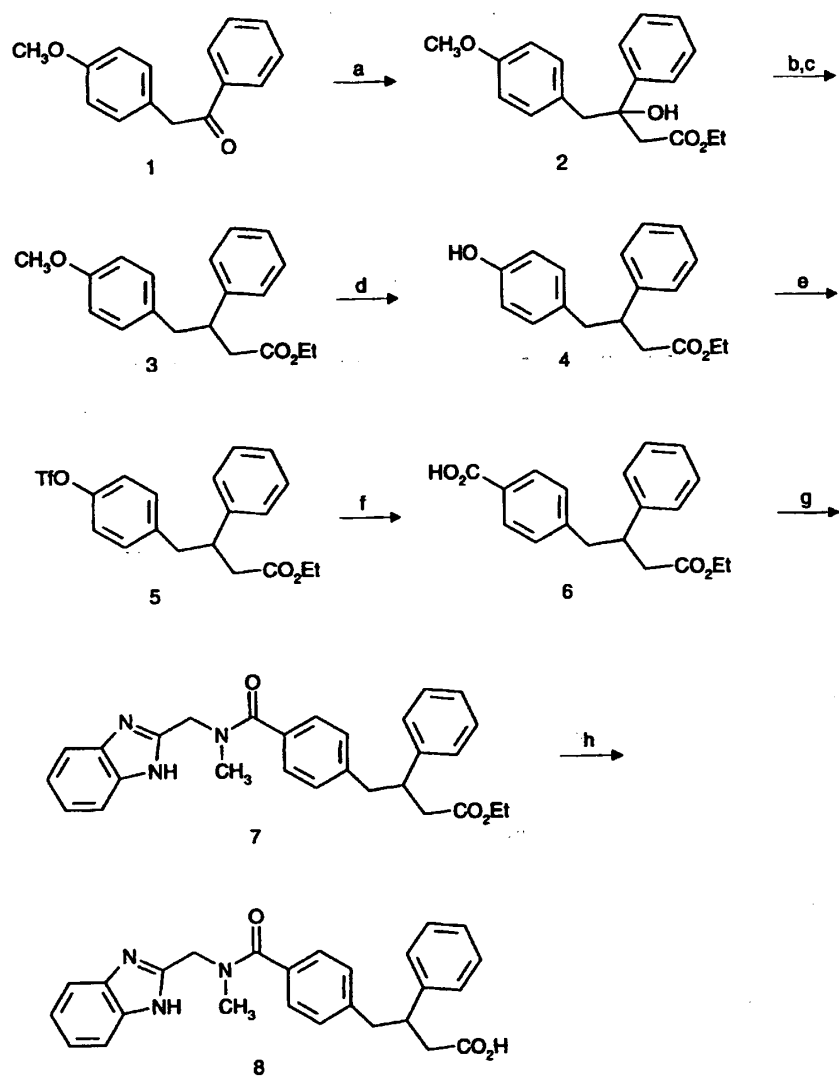
- Compounds wherein V is  $\text{CH}_2\text{CHOH}$  may be obtained from a suitably
- 15 protected compound where V is  $\text{CH}=\text{CH}$  by hydroboration and basic oxidation as disclosed in *Tet. Lett.*, 31, 231 (1990).

The core 6-7 fused ring system is prepared of formula (VI) by methods well known in the art, e.g., Hynes, *et al.*, *J. Het. Chem.*, 1988, 25, 1173; Muller, *et al.*, *Helv. Chim. Acta.*, 1982, 65, 2118; Mori, *et al.*, *Heterocycles*, 1981, 16, 1491.

- 20 Similarly, methods for preparing benzazepines, 1,4-benzothiazepines, 1,4-benzoxazepines and 1,4-benzodiazepines are known and are disclosed, for instance, in Bondinell, *et al.*, International Patent Application WO 93/00095.

The schemes which follow detail the preparation of the compounds of the instant invention.

## Scheme I



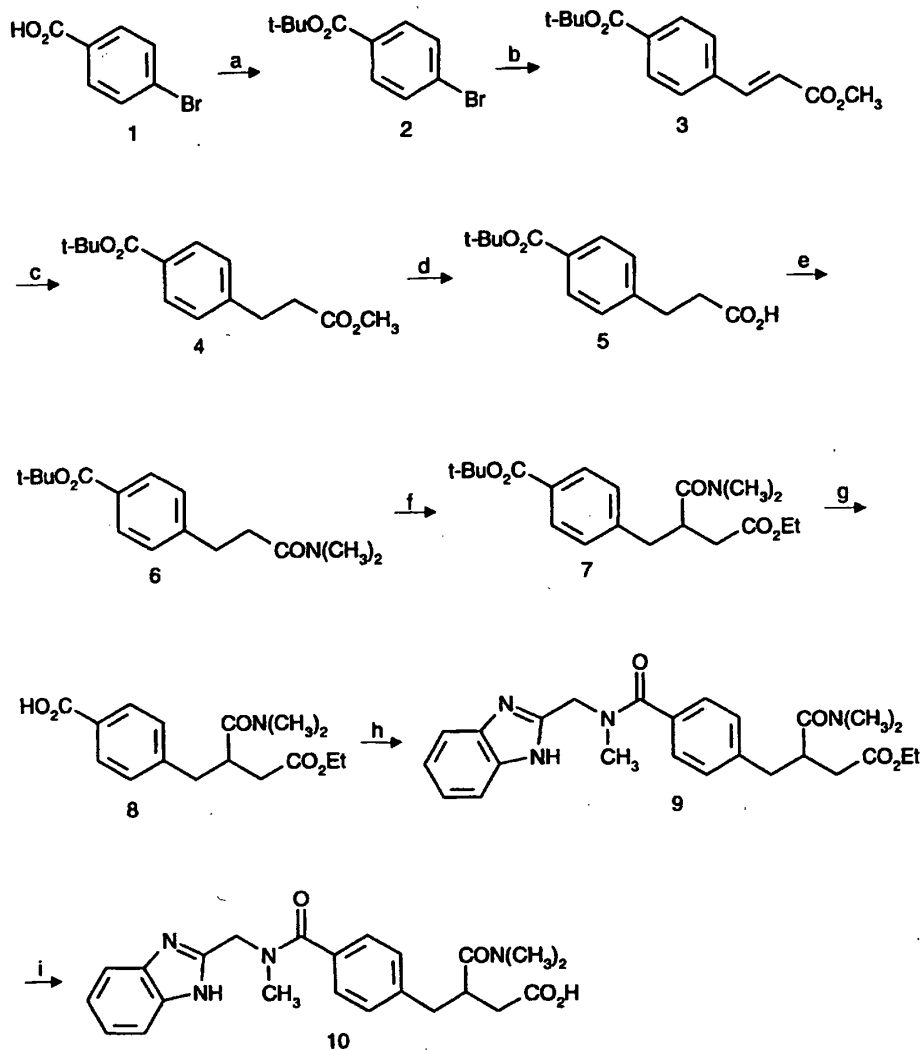
- a)  $\text{EtOAc/LiN(TMS)}_2$ , THF; b)  $\text{Et}_3\text{SiH}$ ,  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; c)  $\text{H}_2$ , 10% Pd/C, EtOH;  
 d)  $\text{EtSH}$ ,  $\text{AlCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; e)  $\text{Tf}_2\text{O}$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ; f)  $\text{CO}$ ,  $\text{KOAc}$ ,  $\text{Pd(OAc)}_2$ ,  
 5 dppe, DMSO; g) 2-(methylaminomethyl)benzimidazole dihydrochloride, EDC,  
 $\text{HOBT} \cdot \text{H}_2\text{O}$ ,  $(i\text{-Pr})_2\text{NEt}$ ,  $\text{CH}_3\text{CN}$ ; h) 1.0 N NaOH, EtOH.

An appropriately substituted deoxybenzoin, such as 2-(4-methoxyphenyl)-1-phenylethanone (*Chem. Ber.* 1958, 91, 755-759), is reacted in an aldol-type reaction with the enolate of ethyl acetate, which can be generated from ethyl acetate on exposure to an appropriate amide base, for instance lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LiN(TMS)<sub>2</sub>), to afford I-2. Frequently, THF is the solvent of choice for an aldol reaction, although THF in the presence of various additives, for instance HMPA or TMEDA, is often used. Reaction of I-2 with triethylsilane (Et<sub>3</sub>SiH) in the presence of boron trifluoride etherate (BF<sub>3</sub> · OEt<sub>2</sub>) according to the general protocol of Orphanopoulos and Smonu (*Synth. Commun.* 1988, 833) for the reduction of tertiary benzylic alcohols affords I-3, together with the olefinic product derived from β-elimination of the alcohol. The olefinic product can be conveniently converted to I-3 by hydrogenation over a palladium catalyst, such as palladium metal on activated carbon (Pd/C), in an appropriate inert solvent, for instance methanol, ethanol, or ethyl acetate. Removal of the methyl ether of I-3 to give I-4 can be accomplished by reaction with ethanethiol (EtSH) in the presence of a Lewis acid catalyst, preferably anhydrous aluminum trichloride (AlCl<sub>3</sub>), in an inert solvent, for instance CH<sub>2</sub>Cl<sub>2</sub>. Other useful methods for removal of a methyl ether are described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Alcohol I-4 is converted to its trifluoromethanesulfonate ester I-5 by reaction with trifluoromethanesulfonic anhydride (Tf<sub>2</sub>O) in the presence of a suitable non-nucleophilic amine base, such as 2,6-lutidine, in an inert solvent, generally CH<sub>2</sub>Cl<sub>2</sub>. I-5 reacts with carbon monoxide (CO) in the presence of potassium acetate, 1,1'-bis(diphenylphosphino)ferrocene (dppf), and a palladium catalyst, for instance palladium acetate (Pd(OAc)<sub>2</sub>), in a suitable solvent, preferably DMSO, according to the general method described by Cacchi and Lupi (*Tet. Lett.* 1992, 33, 3939) for the carboxylation of aryl trifluoromethanesulfonates. The resulting benzoic acid derivative I-6 is converted to an activated form of the carboxylic acid using, for example, EDC and HOBt, or SOCl<sub>2</sub>, and the activated form is subsequently reacted with an appropriate amine, for instance 2-(methylaminomethyl)methylbenzimidazole dihydrochloride, in a suitable solvent



- such as DMF,  $\text{CH}_2\text{Cl}_2$ , or  $\text{CH}_3\text{CN}$ , to afford I-7. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine ((i-Pr)<sub>2</sub>NEt) or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as
- 5 "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). The ethyl ester of I-7 is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or
- 10 HCl, to afford the carboxylic acid I-8. Alternatively, the intermediate carboxylate salt can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

## Scheme II

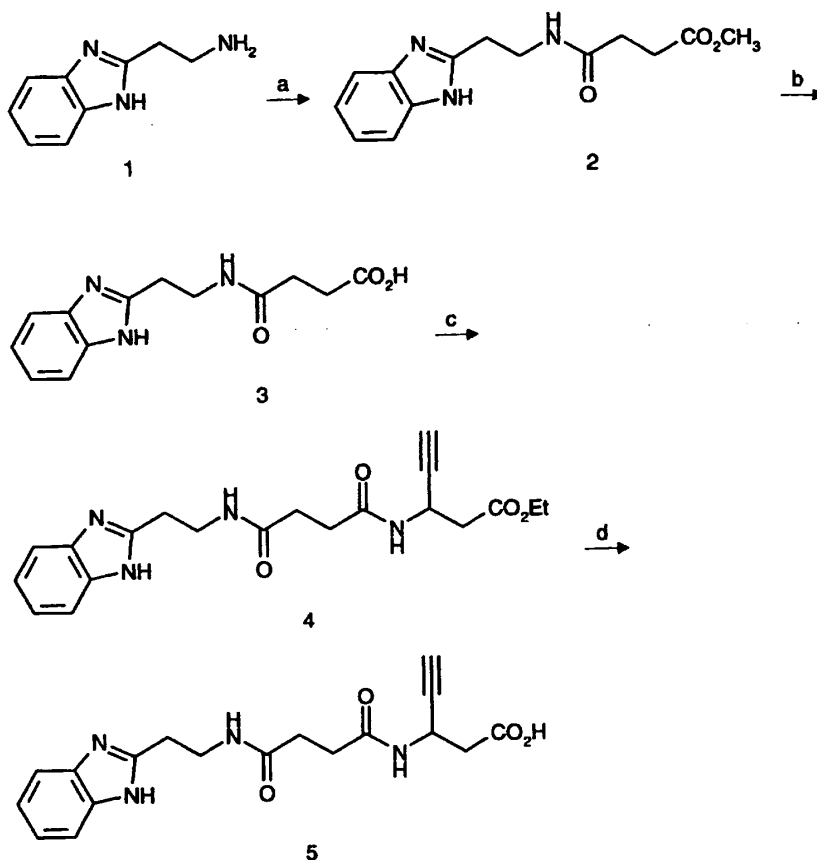


- 5 a) isobutylene, TfOH,  $\text{CH}_2\text{Cl}_2$ ; b) methyl acrylate,  $\text{Pd}(\text{OAc})_2$ ,  $\text{P}(\text{tol})_3$ ,  $(i\text{-Pr})_2\text{NEt}$ , propionitrile; c)  $\text{H}_2$ , 10%  $\text{Pd/C}$ ,  $\text{MeOH}$ ,  $\text{EtOAc}$ ; d) 1.0 N  $\text{LiOH}$ ,  $\text{THF}$ ,  $\text{H}_2\text{O}$ ; e) dimethylamine hydrochloride, EDC,  $\text{HOBt} \cdot \text{H}_2\text{O}$ ,  $(i\text{-Pr})_2\text{NEt}$ ,  $\text{CH}_3\text{CN}$ ; f)  $\text{LiN}(\text{TMS})_2$ ,  $\text{THF}$ , then  $\text{BrCH}_2\text{CO}_2\text{Et}$ ; g)  $\text{TFA}$ ,  $\text{CH}_2\text{Cl}_2$ ; h) 2-(methylaminomethyl)benzimidazole dihydrochloride, EDC,  $\text{HOBt} \cdot \text{H}_2\text{O}$ ,  $(i\text{-Pr})_2\text{NEt}$ ,  $\text{CH}_3\text{CN}$ ; i) 1.0 N  $\text{LiOH}$ ,  $\text{THF}$ ,  $\text{H}_2\text{O}$ .

Commercially available 4-bromobenzoic acid (**II-1**) is converted to the tert-butyl ester **II-2** by reaction with isobutylene in the presence of a catalytic amount of an acid, such as trifluoromethanesulfonic acid (TfOH) or sulfuric acid, in an inert solvent, generally  $\text{CH}_2\text{Cl}_2$  or diethyl ether. Alternative methods for the formation of tert-butyl esters are described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Other esters can be employed, as long as they are compatible with the subsequent chemistry and can be removed selectively when desired. A Heck-type reaction between **II-2** and methyl acrylate affords **II-3**. The general conditions for the Heck reaction have been reviewed by Heck (*Org. Reactions* **1982**, 27, 345). For **II-2**, reaction with methyl acrylate in the presence of palladium (II) acetate ( $\text{Pd}(\text{OAc})_2$ ) and tri-ortho-tolylphosphine ( $\text{P}(\text{tol})_3$ ) in an inert solvent, such as  $\text{CH}_3\text{CN}$ , propionitrile, or toluene, in the presence of an appropriate acid scavenger, such as diisopropylethylamine ( $(i\text{-Pr})_2\text{NEt}$ ), affords **II-3**. Reduction of the  $\alpha,\beta$ -unsaturated ester of **II-3** to afford the saturated compound **II-4** occurs under standard hydrogenation conditions, for instance reaction with hydrogen gas in the presence of a suitable catalyst, preferably palladium metal on activated carbon ( $\text{Pd/C}$ ), in an inert solvent, generally methanol, ethanol, ethyl acetate, or mixtures thereof. The methyl ester of **II-4** is hydrolyzed using aqueous base, for example,  $\text{LiOH}$  in aqueous THF or  $\text{NaOH}$  in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or  $\text{HCl}$ , to afford the carboxylic acid **II-5**. This is converted to an activated form of the carboxylic acid using, for example, EDC and HOBt, or  $\text{SOCl}_2$ , and the activated form is subsequently reacted with an appropriate amine, for instance dimethylamine hydrochloride, in a suitable solvent such as DMF,  $\text{CH}_2\text{Cl}_2$ , or  $\text{CH}_3\text{CN}$ , to afford **II-6**. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine ( $(i\text{-Pr})_2\text{NEt}$ ) or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Reaction of **II-6** with an amide base, for

- instance lithium bis(trimethylsilyl)amide (LiN(TMS)<sub>2</sub>), sodium bis(trimethylsilyl)amide (NaN(TMS)<sub>2</sub>), potassium bis(trimethylsilyl)amide (KN(TMS)<sub>2</sub>), or lithium diisopropylamide (LDA), in an inert solvent, generally THF or ethylene glycol dimethyl ether (DME), affords an intermediate amide enolate.
- 5 This is generally not isolated, but rather is reacted in situ with an electrophile, for example ethyl bromoacetate, to afford the alkylated product **II-7**. Various additives known to those of skill in the art, for instance HMPA, tetramethylethylenediamine (TMEDA), or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), can be used to improve the efficiency of the alkylation reaction. ). The tert-butyl ester
- 10 group of **II-7** is removed under acidic conditions, generally with TFA or HCl, in an inert solvent, usually CH<sub>2</sub>Cl<sub>2</sub>, 1,4-dioxane, or mixtures thereof, to afford the acid **II-8**. Other useful methods for the removal of tert-butyl esters are described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). **II-8** is converted to **II-9** under the general conditions described in Scheme I for the
- 15 conversion of **I-6** to **I-7**, and **II-9** is converted to **II-10** by the general conditions described in Scheme I for the conversion of **I-7** to **I-8**.

## Scheme III

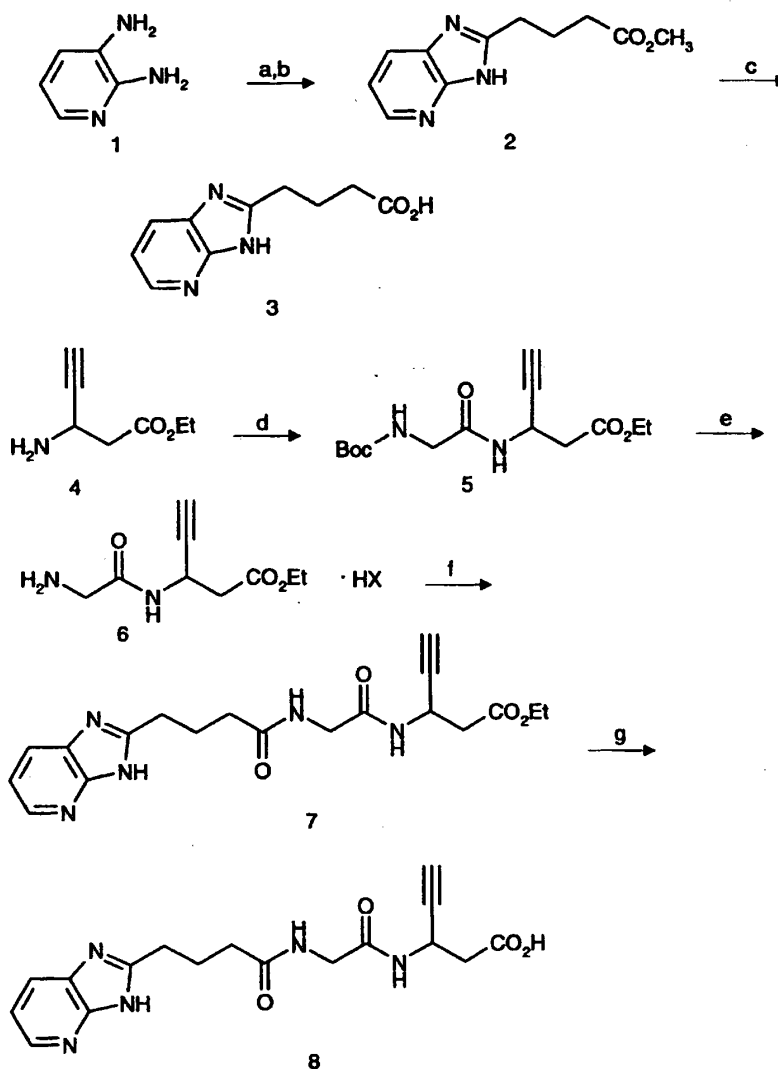


- 5 a) 3-carbomethoxypropionyl chloride, (i-Pr)<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>; b) 1.0 N NaOH, MeOH;  
 c) ethyl 3-amino-4-pentynoate, EDC, HOBT · H<sub>2</sub>O, (i-Pr)<sub>2</sub>NEt, CH<sub>3</sub>CN, DMF; d) 1.0  
 N LiOH, THF, H<sub>2</sub>O, CH<sub>3</sub>CN.

Readily available 2-(2-aminoethyl)benzimidazole is reacted with 3-  
 10 carbomethoxypropionyl chloride in the presence of an appropriate acid scavenger,  
 such as triethylamine, diisopropylethylamine, or pyridine, in a neutral solvent,  
 generally CH<sub>2</sub>Cl<sub>2</sub>, to afford **III-2**. The methyl ester of **III-2** can be hydrolyzed to  
 afford **III-3** under the general conditions described in Scheme 1 for the conversion

- of I-7 to I-8. Alternatively, III-1 can be reacted with succinic anhydride in the presence of an appropriate base, such as triethylamine, diisopropylethylamine, or pyridine, in a neutral solvent, generally  $\text{CH}_2\text{Cl}_2$ , to afford III-3 directly. III-3 is converted to III-4 by reaction with the known ethyl 3-amino-4-pentynoate
- 5 (WO93/07867) under the general conditions described in Scheme I for the conversion of I-6 to I-7. Hydrolysis of the ethyl ester of III-4 to provide III-5 is accomplished according to the general conditions conditions described in Scheme I for the conversion of I-7 to I-8.

## Scheme IV



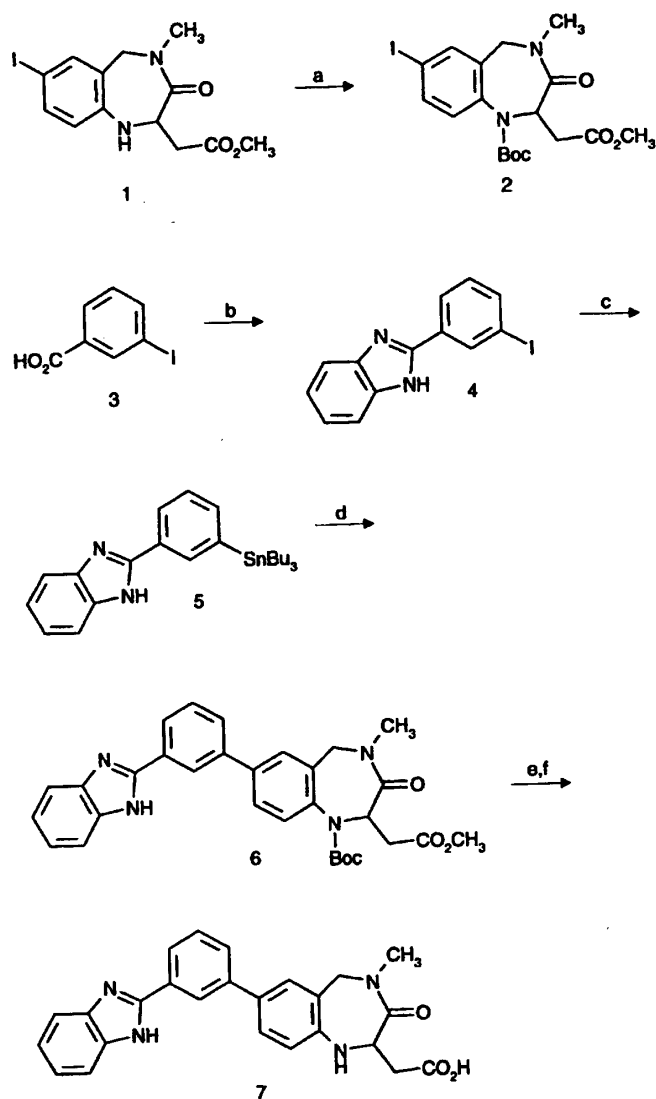
- a) methyl 4-(chloroformyl)butyrate,  $\text{Et}_3\text{N}$ , THF; b) AcOH; c) 1.0 N NaOH, MeOH;  
 d) Boc-Gly, EDC, HOBT  $\cdot$   $\text{H}_2\text{O}$ ,  $(i\text{-Pr})_2\text{NEt}$ ,  $\text{CH}_3\text{CN}$ ; e) TFA,  $\text{CH}_2\text{Cl}_2$ ; f) 3, EDC,  
 5 HOBT  $\cdot$   $\text{H}_2\text{O}$ ,  $(i\text{-Pr})_2\text{NEt}$ ,  $\text{CH}_3\text{CN}$ ; g) 1.0 N LiOH, THF,  $\text{H}_2\text{O}$ .

The synthesis of IV-8 is accomplished by the reaction of two separately prepared intermediates, IV-3 and IV-6. The preparation of intermediate IV-3 begins

with commercially available 2,3-diaminopyridine (IV-1). According to this scheme, IV-1 is acylated with methyl 4-(chloroformyl)butyrate in the presence of a suitable acid scavenger, such as triethylamine, diisopropylethylamine, or pyridine, in a neutral solvent, generally  $\text{CH}_2\text{Cl}_2$  or THF, to afford an intermediate monoacylated derivative. This derivative is then cyclized, for example using refluxing acetic acid, to afford IV-2. Hydrolysis of the methyl ester of IV-2 under the general conditions described in Scheme 1 for the conversion of I-7 to I-8 affords IV-3. The preparation of the intermediate IV-6 begins with the coupling of the known ethyl 3-amino-4-pentynoate (WO93/07867) with commercially available tert-butoxycarbonylglycine (Boc-Gly) under standard peptide bond forming conditions described in the previously referenced Bodansky publication, and in Scheme 1 for the conversion of I-6 to I-7. The product of this reaction, IV-5, is deprotected to IV-6 under acidic conditions which are known to effect removal of a Boc protecting group. Such conditions are described in the previously referenced Bodansky and Greene publications. The two intermediates IV-3 and IV-6 are coupled under standard peptide coupling conditions as previously described to afford IV-7, which is hydrolyzed to IV-8 according to the general methods described in Scheme 1 for the conversion of I-7 to I-8.



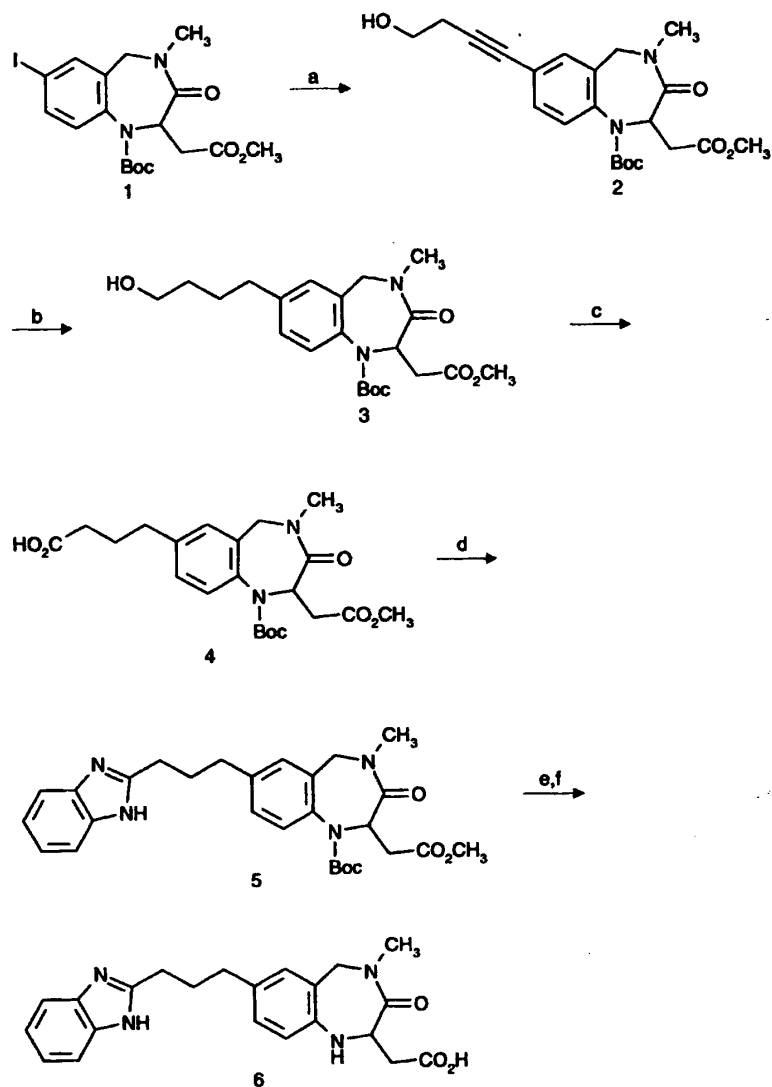
## Scheme V



- 5 a)  $(\text{Boc})_2\text{O}$ , DMAP,  $\text{CH}_3\text{CN}$ ; b) isobutylchloroformate,  $\text{Et}_3\text{N}$ , THF, then 1,2-phenylenediamine, then  $\text{AcOH}$ ; c)  $(n\text{-Bu}_3\text{Sn})_2$ ,  $(\text{PPh}_3)_2\text{PdCl}_2$ , DMF; d)  $\text{CuI}$ ,  $(\text{PPh}_3)_2\text{PdCl}_2$ , DMF; e) 4 M  $\text{HCl}$ /dioxane; f) 1.0 N  $\text{NaOH}$ ,  $\text{MeOH}$ .

The synthesis of V-7 is accomplished by the reaction of two separately prepared intermediates, V-2 and V-5. V-2 is conveniently prepared by reaction of the readily available V-1 with di-tert-butyl dicarbonate ((Boc)<sub>2</sub>O) in the presence of an acylation catalyst, preferably 4-dimethylaminopyridine (DMAP) or 4-pyrrolidinopyridine, in a neutral solvent, for example CH<sub>3</sub>CN, THF, or CH<sub>2</sub>Cl<sub>2</sub>. The preparation of intermediate V-5 begins with commercially available 3-iodobenzoic acid (V-3), which is converted to the benzimidazole derivative V-4. According to this scheme, V-3 is reacted with isobutyl chloroformate in the presence of a suitable amine base, such as triethylamine, diisopropylethylamine, or 4-methylmorpholine, in a neutral solvent, generally CH<sub>2</sub>Cl<sub>2</sub> or THF, to afford an intermediate mixed anhydride derivative. Without isolation, this derivative is reacted with an appropriate phenylenediamine to produce a mono-N-acylated phenylenediamine intermediate. This intermediate is then cyclized to V-4 using acetic acid. Reaction of V-4 with bis(tributyltin) to produce V-5 occurs under palladium catalysis using, for example bis(triphenylphosphine)palladium (II) chloride ((PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>), in an inert solvent, usually DMF. Stille-type coupling of V-2 with V-5 to afford V-6 is mediated by a palladium catalyst, for instance bis(triphenylphosphine)palladium (II) chloride ((PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>), in the presence of copper (I) iodide (CuI), in a suitable neutral solvent, generally DMF. To obtain V-7, the protecting groups of V-6 are removed by well-established methods known to those of skill in the art and described in the previously cited Greene publication. Thus, the Boc protecting group is removed under acidic conditions, such as 4 M HCl in dioxane or TFA in CH<sub>2</sub>Cl<sub>2</sub>, and the methyl ester is hydrolyzed as generally described in Scheme 1 for the conversion of I-7 to I-8.

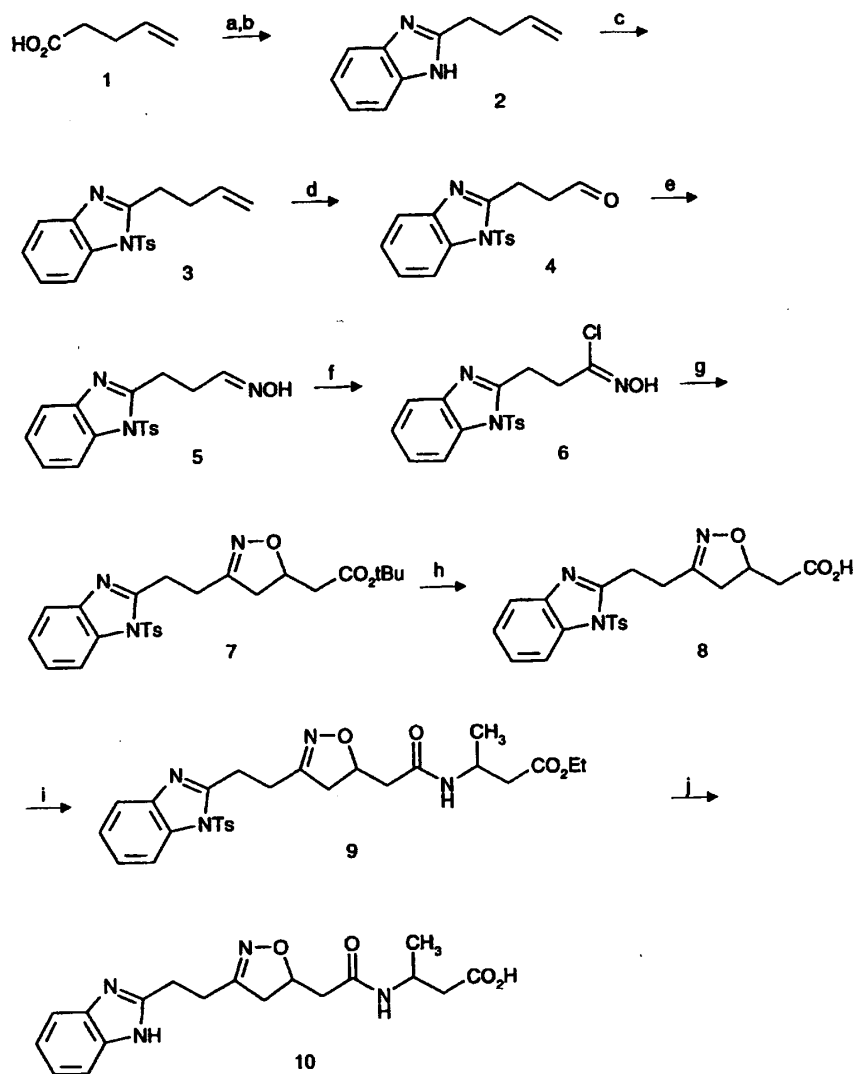
## Scheme VI



- 5 a) 3-butyne-1-ol,  $(\text{PPh}_3)_2\text{PdCl}_2$ ,  $\text{PPh}_3$ ,  $\text{CuI}$ ,  $\text{Et}_3\text{N}$ ; b)  $\text{H}_2$ , 10%  $\text{Pd/C}$ ,  $\text{EtOH}$ ; c) 2,2,6,6-tetramethyl-oxopiperidinium chloride,  $\text{CH}_2\text{Cl}_2$ , then  $\text{NaClO}_2$ ,  $\text{Na}_2\text{HPO}_4$ , 2-methyl-2-butene,  $\text{H}_2\text{O}$ ; d) isobutyl chloroformate,  $\text{Et}_3\text{N}$ , then 1,2-phenylenediamine, then  $\text{AcOH}$ ; e) 1.0 N  $\text{LiOH}$ ,  $\text{THF}$ ,  $\text{H}_2\text{O}$ ; f)  $\text{TFA}$ ,  $\text{CH}_2\text{Cl}_2$ .

Compound **VI-1**, the preparation of which is described in Scheme V, is reacted with 3-butyne-1-ol in the presence of a catalytic amount of a palladium salt, usually bis(triphenylphosphine)palladium (II) chloride ((PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>), together with a catalytic amount of copper (I) iodide (CuI), in an amine solvent, such as triethylamine (Et<sub>3</sub>N), to afford **VI-2**. A phosphine ligand, such as triphenylphosphine (PPh<sub>3</sub>), can be added to improve the efficiency of the reaction. Reduction of the acetylenic unit of **VI-2** is accomplished under standard hydrogenation conditions which are well-known to those of skill in the art. The resulting compound, **VI-3**, is oxidized to the corresponding carboxylic acid **VI-4**, by the two-step method described by Wovkulich (*J. Org. Chem.* **1993**, 58, 832-839). Many alternative methods for the oxidation of a primary alcohol to the corresponding carboxylic acid have been described, and can be found in such reference volumes as "Compendium of Organic Synthetic Methods" (published by Wiley-Interscience). Conversion of the carboxylic acid of **VI-4** to the benzimidazole derivative **VI-5** follows the procedures described in the above Schemes. The methyl ester of **VI-5** is removed as described in the above Schemes, and the Boc protecting group is removed under acidic conditions, such as 4 M HCl in dioxane or TFA in CH<sub>2</sub>Cl<sub>2</sub>, to afford **VI-6**.

## Scheme VII

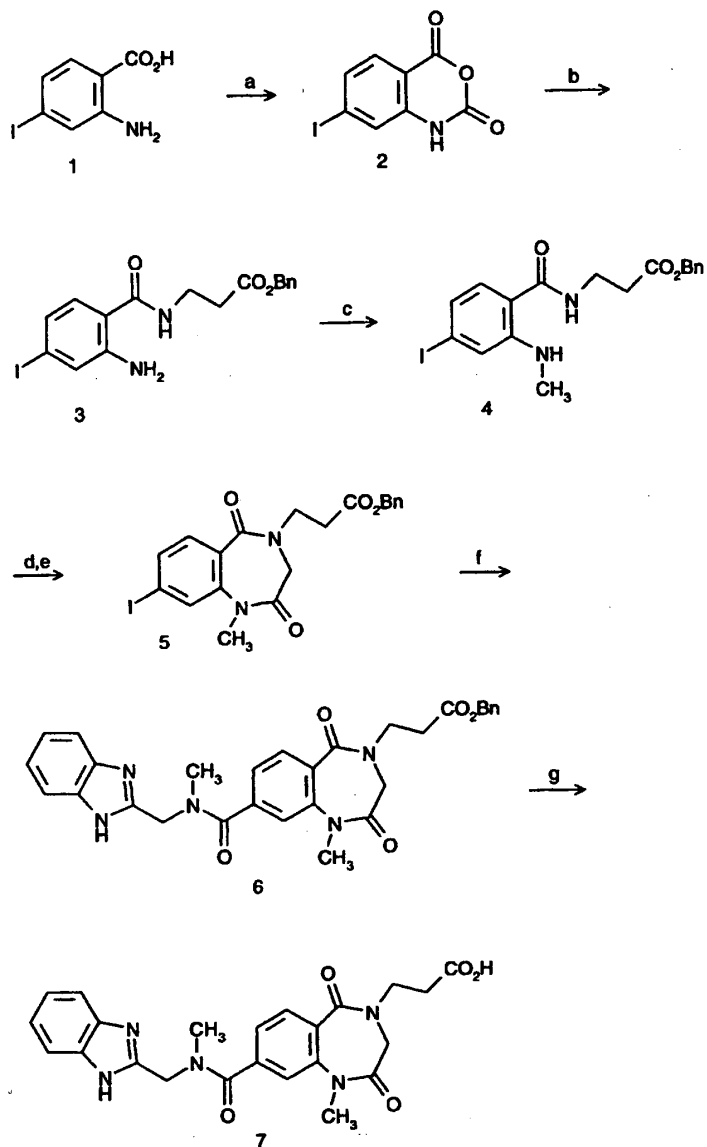


- a) 1,2-phenylenediamine, DCC, DMF,  $\text{CH}_2\text{Cl}_2$ ; b) AcOH, THF; c) TsCl, NaH, THF;  
 5 d)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ , MeOH, then DMS; e)  $\text{NH}_2\text{OH} \cdot \text{HCl}$ , NaOAc, MeOH; f) NCS, DMF;  
 g) tert-butyl 3-butenolate,  $\text{Et}_3\text{N}$ ; h) 4 M HCl/dioxane,  $\text{CH}_2\text{Cl}_2$ ; i) ethyl 3-aminobutyrate, EDC, HOBT  $\cdot \text{H}_2\text{O}$ ,  $(i\text{-Pr})_2\text{NEt}$ ,  $\text{CH}_3\text{CN}$ ; j) 1.0 N LiOH, THF,  $\text{H}_2\text{O}$ .

Commercially available 4-pentenoic acid (VII-1) is converted to the benzimidazole derivative VII -2 using to the general procedures described previously. Protection of one of the nitrogen atoms of the benzimidazole moiety in VII -2 can be accomplished by reaction with a sulfonyl chloride, for instance p-toluenesulfonyl chloride, in the presence of a suitable base, generally sodium hydride or an aqueous alkali metal hydroxide, in an inert solvent, preferably THF, to afford VII -3. Alternative protecting groups known to those of skill in the art may be used, as long as they are compatible with the subsequent chemistry and can be removed when desired. Such protecting groups are described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Oxidative cleavage of the olefin of VII -3 to afford the aldehyde VII -4 can be conveniently accomplished by ozonolysis in an inert solvent, usually  $\text{CH}_2\text{Cl}_2$  or a mixture of  $\text{CH}_2\text{Cl}_2$  and MeOH, followed by in-situ reduction of the ozonide with a suitable reducing agent, generally dimethylsulfide (DMS) or triphenylphosphine. Alternative methods for oxidative cleavage, such as the Lemieux-Johnson reaction (*J. Org. Chem.* 1956, 21, 478) can also be used. The aldehyde is converted to the aldoxime VII -5 by standard procedures known to those of skill in the art, and this aldoxime is oxidized to the oximinoyl chloride derivative VII -6 by the methods described in WO 95/14682 and WO 95/14683. Reaction of VII -6 with an olefin, such as tert-butyl 3-butenate (*Tet. Lett.* 1985, 26, 381-384), in the presence of a suitable base, for instance triethylamine or diisopropylethylamine, in an inert solvent such as benzene or toluene, according to the protocol described in WO 95/14682 and WO 95/14683, gives the cycloadduct I-7. The tert-butyl ester of VII -7 is removed under standard acidic conditions, generally TFA in  $\text{CH}_2\text{Cl}_2$  or HCl in dioxane, to give the carboxylic acid VII -8. The carboxylic acid is activated using, for example, EDC and HOBt, or  $\text{SOCl}_2$ , and the activated form is subsequently reacted with an appropriate amine, for instance a suitable derivative of  $\beta$ -alanine, in a neutral solvent, such as DMF,  $\text{CH}_2\text{Cl}_2$ , or  $\text{CH}_3\text{CN}$ , to afford VII -9. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine ((i-Pr)<sub>2</sub>NEt) or pyridine, may be used. Many additional methods for converting a

carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Derivatives of  $\beta$ -alanine are readily available in either racemic or optically pure form by a variety of methods known to those of skill in the art. A representative method is described in WO 93/07867. The ethyl ester and sulfonyl protecting groups of **VII -9** are removed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol. The intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **VII -10**. Alternatively, the intermediate carboxylate salt can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

## Scheme VIII

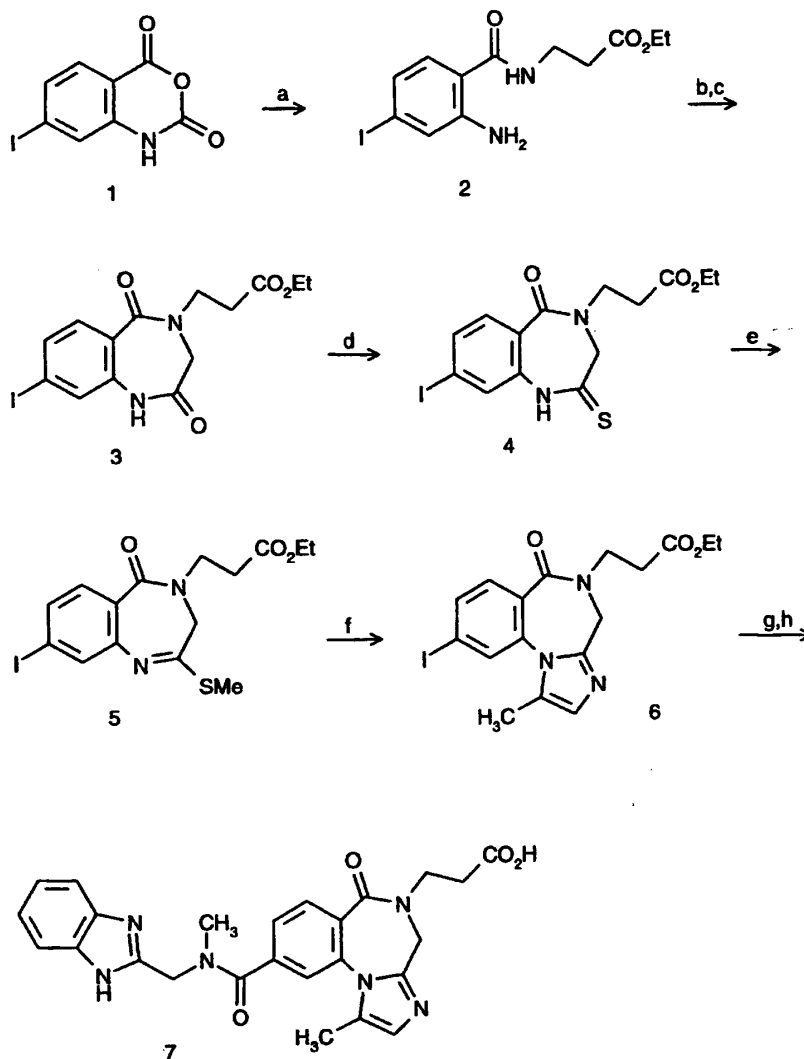


- 5 a)  $\text{COCl}_2$  in toluene,  $\text{Na}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ ; b)  $\beta$ -alanine benzyl ester tosylate, DMAP, pyridine; c)  $\text{CH}_3\text{I}$ , 2,6-lutidine, DMF; d)  $\text{BrCH}_2\text{COBr}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; e)  $\text{NaH}$ , DMF, f)  $\text{CO}$ ,  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ , DIEA, 2-(methylaminomethyl)benzimidazole dihydrochloride, NMP; g)  $\text{H}_2$ , Pd/C, EtOH.



Following the procedures of US 5403836 and WO 9504057, except starting from 2-amino-4-iodobenzoic acid (**VIII-1**) rather than 2-amino-5-iodobenzoic acid, compound **VIII -5** is prepared. Reaction of **VIII -5** with an appropriate amine, for instance 2-(methylaminomethyl)benzimidazole, in a carbon monoxide atmosphere, in the presence of a palladium catalyst, preferably  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ , in an inert solvent, optimally 1-methyl-2-pyrrolidinone (NMP) gives the amide **VIII -6**. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine (DIEA) or pyridine, may be used. The benzyl ester of **VIII -6** is removed to afford **VIII -7** under standard hydrogenolysis conditions well-known to those of skill in the art. Alternatively, the benzyl ester can be saponified using aqueous base, for example, LiOH in aqueous THF, or NaOH in aqueous methanol or ethanol. The intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid. If desired, the intermediate carboxylate salt of **VIII -7** can be isolated, or a suitable salt of the carboxylic acid can be prepared by methods well-known to those of skill in the art.

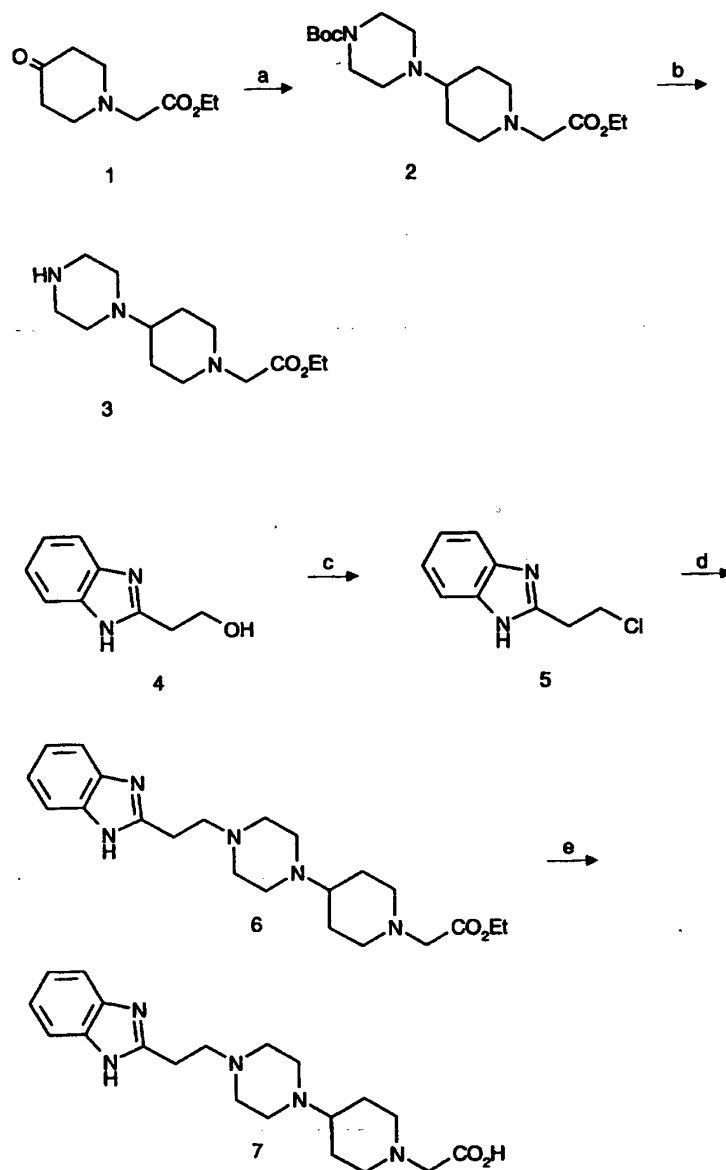
## Scheme IX



- 5 a)  $\beta$ -alanine ethyl ester hydrochloride, DMAP, pyridine; b)  $\text{BrCH}_2\text{COBr}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; c)  $\text{NaH}$ , DMF; d) Lawesson's reagent, THF,  $50^\circ\text{C}$ ; e)  $\text{CH}_3\text{I}$ ,  $(n\text{-Bu})_4\text{NHSO}_4$ ,  $\text{NaOH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{H}_2\text{O}$ ; f) propargylamine, pyridine  $\cdot$   $\text{HCl}$ , toluene; g)  $\text{CO}$ ,  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ , DIEA, 2-(methylaminomethyl)benzimidazole dihydrochloride, NMP; h)  $\text{LiOH}$ , THF,  $\text{H}_2\text{O}$ .

Following the procedures of US 5403836 and WO 9504057, except starting from 4-iodoisatoic anhydride (**IX-1**, see Scheme I) rather than 5-iodoisatoic anhydride, compound **IX-6** is prepared. **IX-6** is converted to **IX-7** following the procedures described in Scheme XIII for the conversion of **XIII -5** to **XIII -7**.

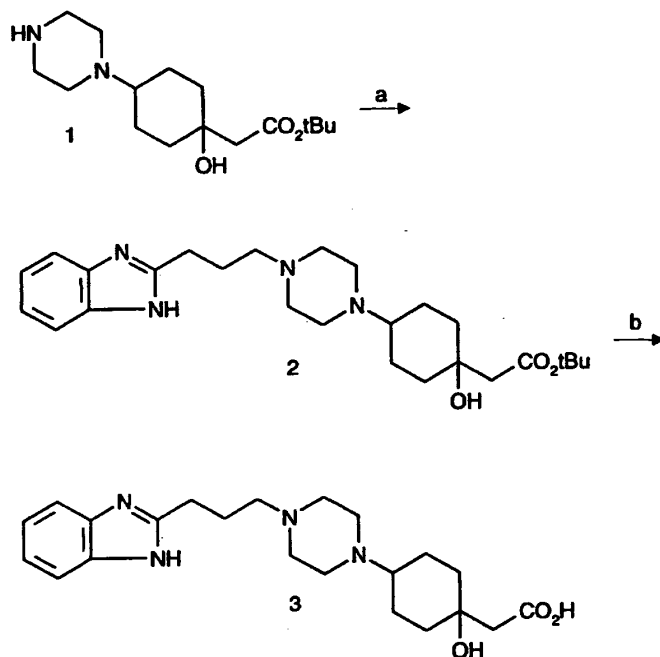
## Scheme X



- 5 a) 1-Boc-piperazine,  $\text{NaBH}_3\text{CN}$ ,  $\text{HCl}$ ,  $\text{MeOH}$ ; b) 4 M  $\text{HCl}$ /dioxane,  $\text{CH}_2\text{Cl}_2$ ; c)  $\text{SOCl}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; d) 3, DIEA, DMF; e) 1.0 N  $\text{NaOH}$ ,  $\text{MeOH}$ .

Reductive amination of the readily available 1-(ethoxycarbonylmethyl)-4-piperidone (X-1, EPA 0 542 363 A2) with commercially available 1-Boc-piperazine and an appropriate reducing agent, preferably sodium cyanoborohydride, affords amine X-2. The reaction is generally conducted under acidic catalysis, usually with HCl, in a hydroxylic solvent, for instance methanol or ethanol. The Boc protecting group is removed under acidic conditions, preferably HCl/dioxane or TFA, in a suitable solvent, such as  $\text{CH}_2\text{Cl}_2$ , to give amine X-3. This reacts with 2-(2-chloroethyl)benzimidazole (X-5) in the presence of an appropriate acid scavenger, for instance diisopropylethylamine (DIEA), in a polar solvent, preferably DMF, to give the coupled product X-6. 2-(2-Chloroethyl)benzimidazole can be prepared from 2-(2-hydroxyethyl)benzimidazole by reaction with a suitable halogenating reagent, such as thionyl chloride, or carbon tetrachloride in the presence of triphenylphosphine, in an inert solvent, for example  $\text{CH}_2\text{Cl}_2$ . The ethyl ester of X-6 is removed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol. The intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid X-7. Alternatively, the intermediate carboxylate salt can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

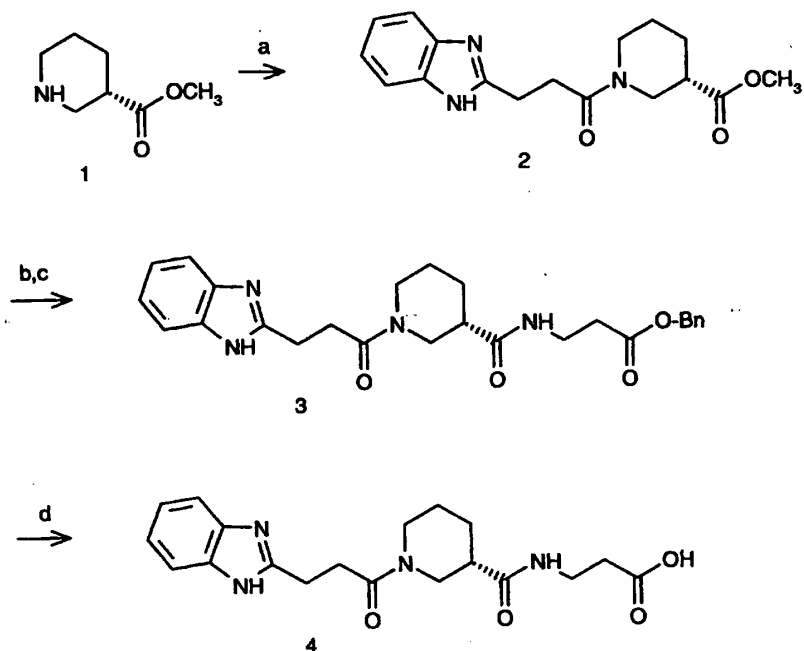
## Scheme XI



- 5 a) 2-(3-bromopropyl)benzimidazole, DIEA, DMF; b) 4 M HCl/dioxane,  $\text{CH}_2\text{Cl}_2$ .

The readily available piperazine derivative XI-1 (EPA 0 537 980 A1) is reacted with the readily available 2-(3-bromopropyl)benzimidazole (*J. Org. Chem.* **1962**, 27, 2165) in the presence of an appropriate acid scavenger, for instance diisopropylethylamine (DIEA), in a polar solvent, preferably DMF, to give the coupled product XI-2. The tert-butyl ester protecting group is removed under standard acidic conditions, preferably HCl/dioxane or TFA, in a suitable solvent, such as  $\text{CH}_2\text{Cl}_2$ , to the carboxylic acid XI-3. If desired an appropriate salt of the carboxylic acid can be prepared by methods well-known to those of skill in the art.

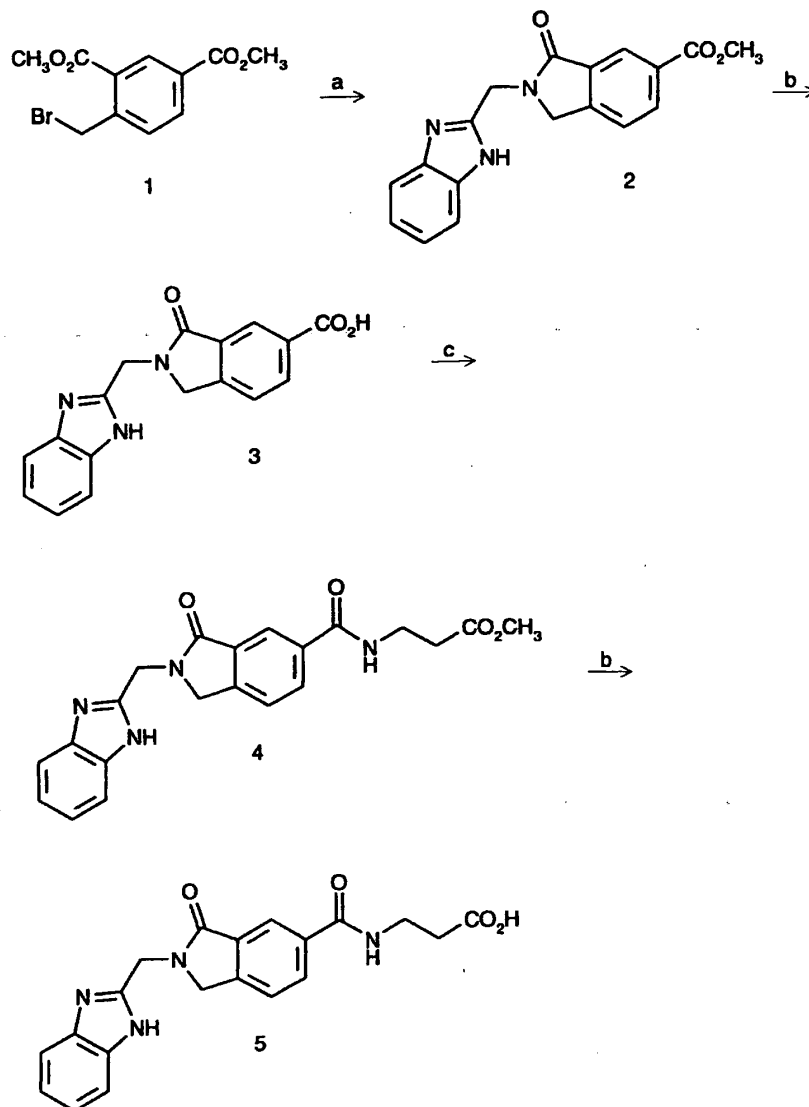
## Scheme XII



- 5 a) 2-(benzimidazolyl)propionic acid, BOP-Cl, NMM,  $\text{CH}_2\text{Cl}_2$ ; b) LiOH, THF,  $\text{H}_2\text{O}$ ;  
 c) benzyl  $\beta$ -alaninate, EDC, HOBT  $\cdot \text{H}_2\text{O}$ , NMM,  $\text{CH}_2\text{Cl}_2$ ; d)  $\text{H}_2$ , 10% Pd/C, AcOH,  
 THF,  $\text{H}_2\text{O}$ .

The procedures of Beavers et. al., WO 95/25091, Example 1, were followed  
 10 to give XII-4, except (2-benzimidazolyl)propionic acid was substituted for  $\text{N}^\alpha$ -Boc-  
 D-lys(Cbz)-OH.

## Scheme XIII

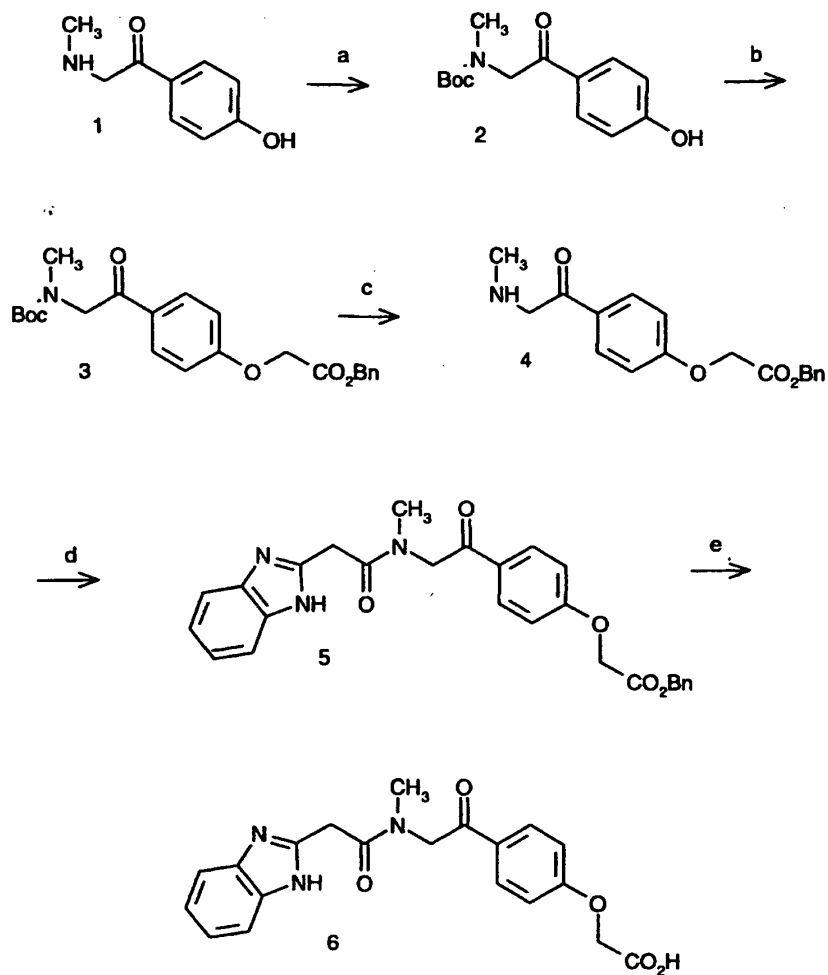


- 5 a) 2-(aminomethyl)benzimidazole, Et<sub>3</sub>N, benzene; b) 1.0 N LiOH, MeOH, H<sub>2</sub>O; c)  $\beta$ -alanine ethyl ester, BOP, Et<sub>3</sub>N, CH<sub>3</sub>CN.



A suitably functionalized amine, such as 2-(aminomethyl)benzimidazole, is reacted with dimethyl 4-bromomethylbenzene-1,3-dicarboxylate (**XIII-1**; synthesized as in EP 0540334A1) under the general conditions described for the preparation of 1-H-isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxy-ethyl)-2-[2-(piperidinyl)ethyl]-3-oxo (preparation 1-12, EPA 0 540 334 A1), to afford **XIII-2**. The methyl ester of **XIII-2** is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **XIII-3**. The carboxylic acid of **XIII-3** is converted to an activated form of the carboxylic acid using, for example, EDC and HOBt, SOCl<sub>2</sub>, or BOP reagent, and the activated form is subsequently reacted with an appropriate amine, for instance β-alanine ethyl ester, in a suitable solvent such as DMF, CH<sub>2</sub>Cl<sub>2</sub>, or CH<sub>3</sub>CN, to afford **XIII-4**. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine ((i-Pr)<sub>2</sub>NEt) or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Ester hydrolysis as described above for the conversion of **XIII-2** to **XIII-3** then affords **XIII-5**. Alternatively, the intermediate carboxylate salt of **XIII-5** can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

## Scheme XIV

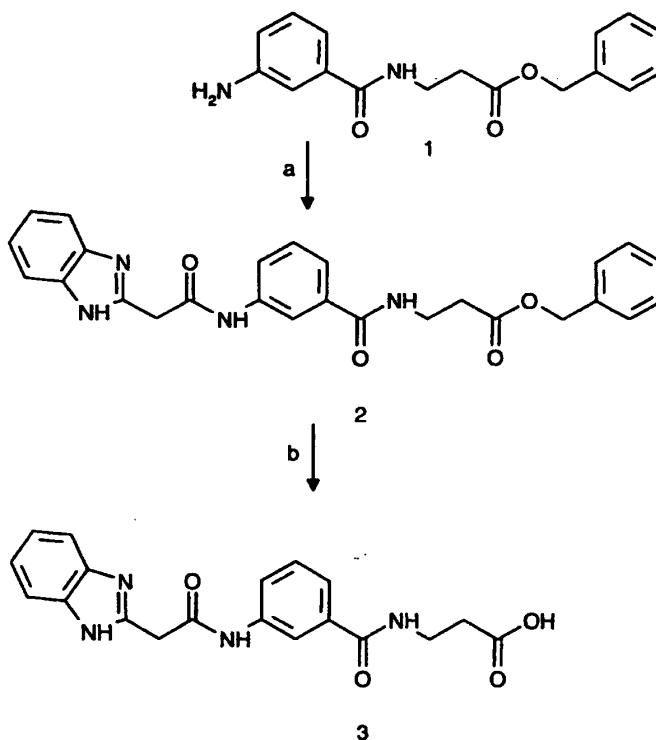


- 5 a)  $(\text{Boc})_2\text{O}$ , NaOH, 1,4-dioxane,  $\text{H}_2\text{O}$ ; b)  $\text{BrCH}_2\text{CO}_2\text{Bn}$ ,  $\text{K}_2\text{CO}_3$ , acetone; c) 4 M HCl/dioxane; d) 2-(benzimidazolyl)acetic acid, EDC, DIEA, DMF; e)  $\text{H}_2$ , 5 % Pd/C, MeOH.

XIV-1 is treated with di-tert-butyl dicarbonate and sodium hydroxide in aqueous dioxane to afford XIV -2, which is alkylated on oxygen with benzyl bromoacetate and potassium carbonate in acetone to give XIV -3. The Boc group in

**XIV -3** is removed with hydrogen chloride in dioxane, and the resulting **XIV -4** is acylated on nitrogen with 2-(benzimidazolyl)acetic acid, EDC and DIEA in DMF to give **XIV -5**. The benzyl ester in **XIV -5** is cleaved by treatment with hydrogen and palladium-on-carbon in methanol to give **XIV -6**.

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Scheme XV

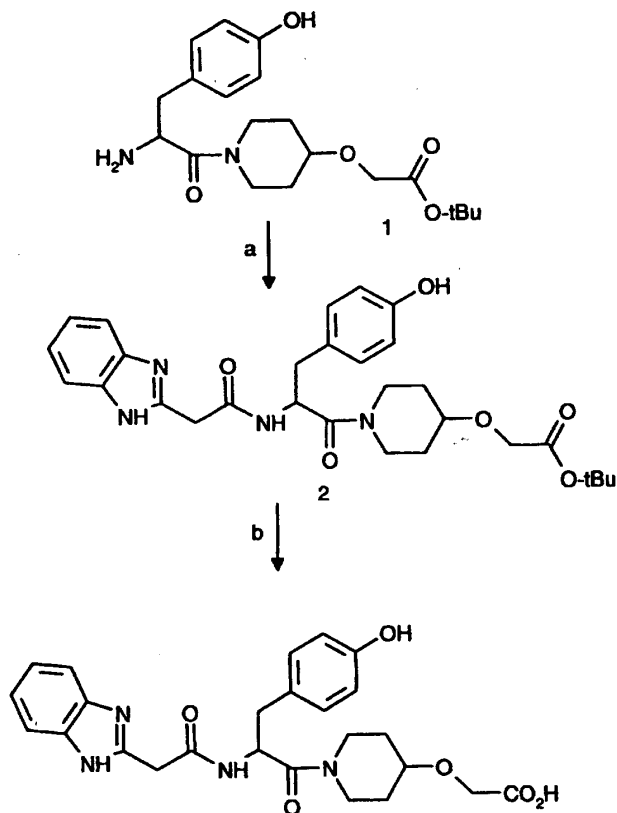
10 a) 2-(benzimidazolyl)acetic acid, EDC, DIEA, DMF; b) NaOH, H<sub>2</sub>O,  
CH<sub>3</sub>OH.

**XI-1**, prepared as described in Alig et. al., EPA 0372486, is condensed with  
a suitable substituted carboxylic acid, such (2-benzimidazolyl)acetic acid, in the  
15 presence of EDC and DIEA, and in a suitable solvent, e.g., DMF or acetonitrile.

- Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthesis". Vol. I-VI (published by Springer-Verlag). Hydrolysis of the ester is accomplished by saponification with a suitable reagent, e.g., sodium hydroxide, in a suitable solvent, e.g., aqueous methanol. Alternatively, a benzyl ester may be converted to the acid by treatment with a suitable catalyst, e.g., Pd/C, and hydrogen in a suitable solvent, e.g., methanol, ethanol or acetic acid.
- 5

Scheme XVI

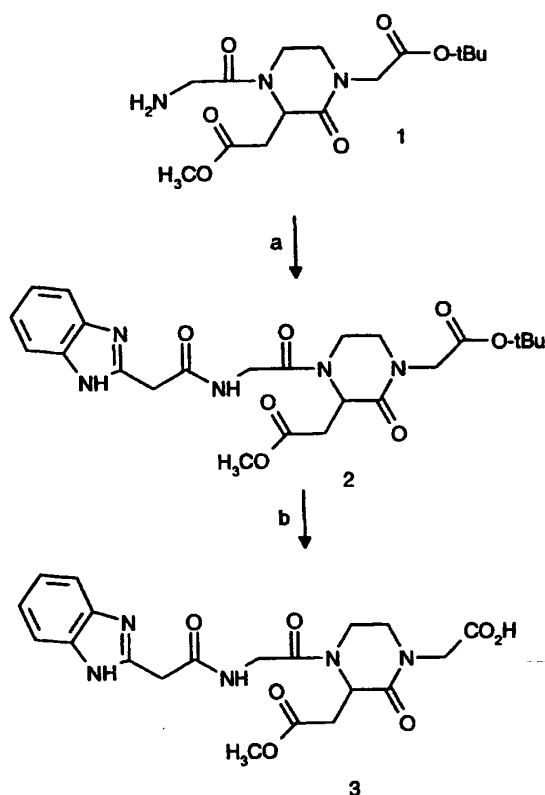
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a) 2-(benzimidazolyl)acetic acid, EDC, DIEA, DMF; b) TFA

**XVI-1**, prepared as described in Alig et. al., EPA 0505868, is condensed with a suitable substituted carboxylic acid, such as (2-benzimidazolyl)acetic acid, in the presence of EDC and DIEA, in a suitable solvent, e.g., DMF or acetonitrile, to give **XVI -2**. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthesis". Vol. I-VI (published by Springer-Verlag). Hydrolysis of the ester in **XVI -2** is accomplished with trifluoroacetic acid or hydrogen chloride to give **XVI -3**. Alternatively, the ester in **XVI -2** may be saponified with a suitable reagent, e.g., 1N NaOH, in a suitable solvent, e.g., methanol.

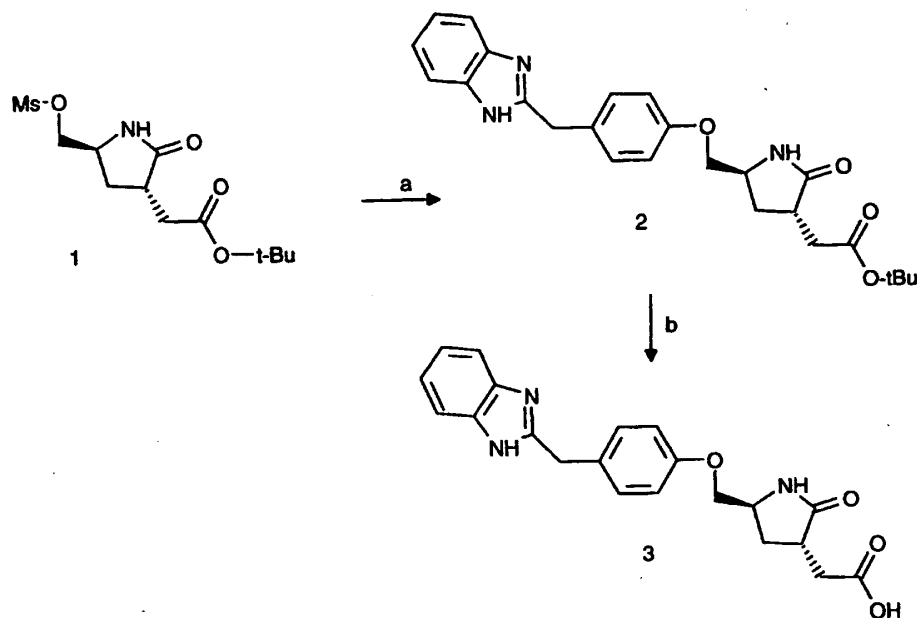
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Scheme XVII

a) 2-(benzimidazolyl)acetic acid, EDC, DIEA, DMF; b) TFA,  $\text{CH}_2\text{Cl}_2$ .

**XVII-1**, prepared as described in Sugihara, et. al., EP 0529858, is condensed with a suitable substituted carboxylic acid, such as (2-benzimidazolyl)acetic acid, to give **XVII-2**, and the tert-butyl ester is cleaved with TFA, following the general procedure of Sugihara, et. al., Example 59, to give **XVII-3**. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthesis", Vol. I-VI (published by Springer-Verlag).

### Scheme XVIII



a) 4-[2-(benzimidazolyl)methyl]phenol,  $\text{Cs}_2\text{CO}_3$ , DMF; b) TFA

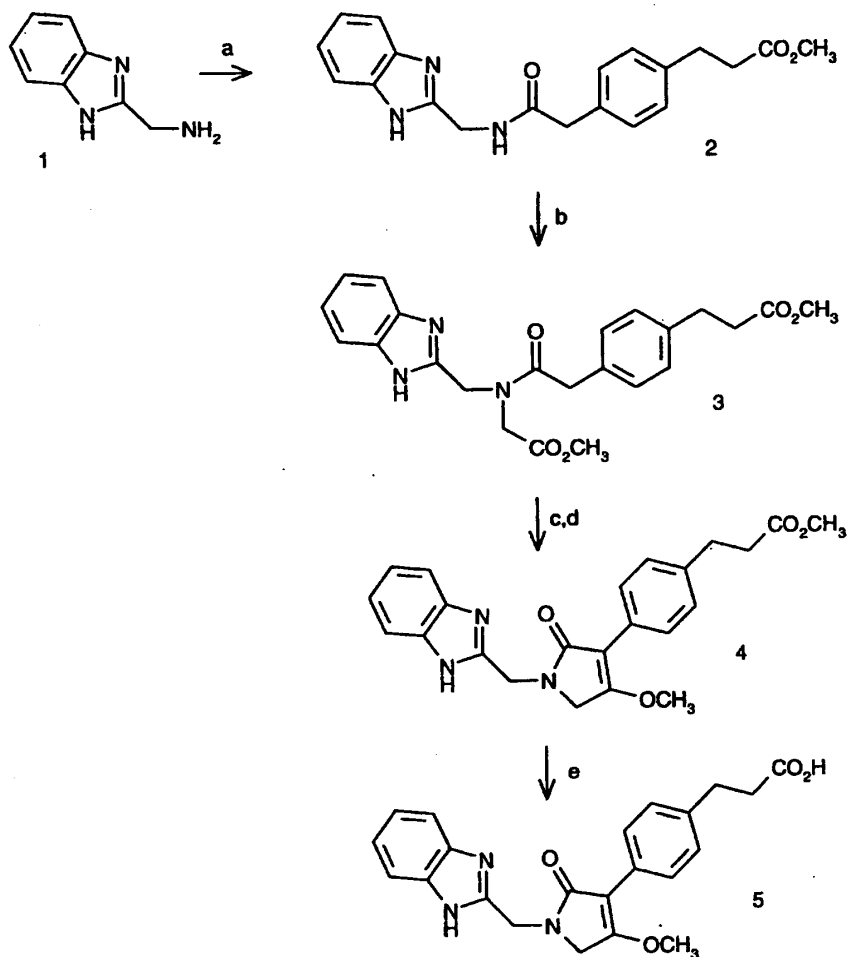
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Compound **XVIII-1**, prepared as described in Himmelsbach, et. al., Australian Patent Application AU-A-86926/91, Example VI(28), is treated with a suitable substituted phenol, such as 4-[2-(benzimidazolyl)methyl]phenol, prepared

by the general procedure of Wahlgren and Addison, J. Heterocycl. Chem., **1989**, 26, 541-3, following the general method of Himmelsbach, et. al., Example 3(51), to give **XVIII -2**. The tert-butyl ester in **XVIII -2** is hydrolyzed with 1N NaOH in CH<sub>3</sub>OH following the general procedure of Himmelsbach, Example 7(3) to give **XVIII -3**.

- 5 Alternatively, the tert-butyl ester may be cleaved with TFA or HCl.

## Scheme XIX

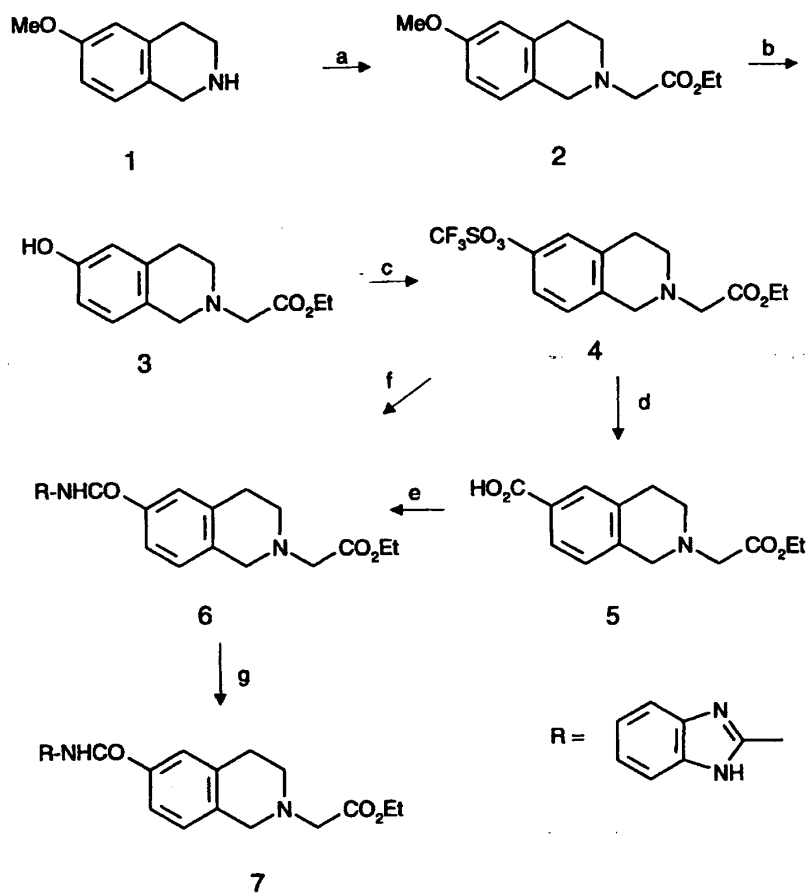


- 5 a)  $\text{HO}_2\text{CCH}_2\text{Ph-4-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$ ,  $\text{Ph}_2\text{POCl}$ ,  $\text{Et}_3\text{N}$ , DMAP, THF; b) NaH, DMF,  $\text{BrCH}_2\text{CO}_2\text{CH}_3$ ; c) KOt-Bu, THF, DMF; d) KOt-Bu,  $\text{CH}_3\text{I}$ , DMF; e) LiOH, THF,  $\text{H}_2\text{O}$ .

The procedures of Linz, et. al., EP 0567968, are used to prepare XIX-5,  
 10 except (2-benzimidazolyl)methanamine is substituted for 4-cyanoaniline.



Scheme XX

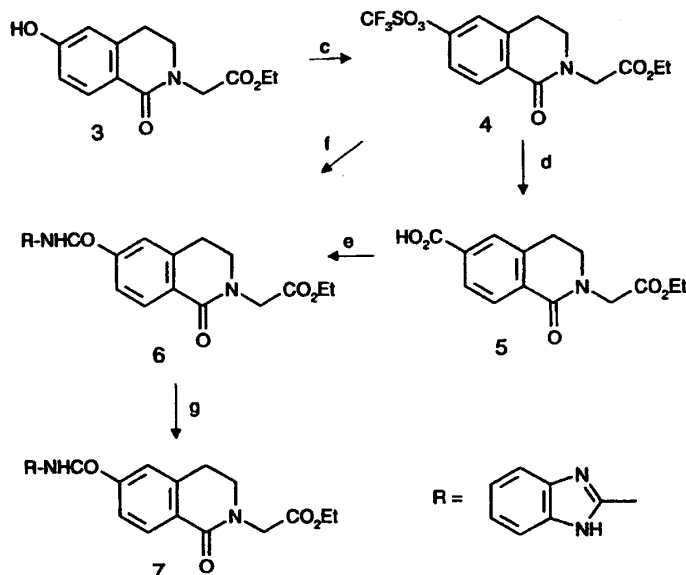


- 5 a)  $\text{ClCH}_2\text{CO}_2\text{Et}$ ,  $\text{Et}_3\text{N}$ , DMF; b)  $\text{BBr}_3$ ; c)  $(\text{CF}_3\text{SO})_2\text{O}$ ; d)  $\text{CO}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , DIEA, NMP,  $\text{NH}_4\text{HCO}_3$ ,  $\text{H}_2\text{O}$ ; e)  $\text{H}_2\text{N-R}$ , EDC / HOBt, DIEA, DMF; f)  $\text{H}_2\text{N-R}$ ,  $\text{CO}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , DIEA, NMP,  $\text{NH}_4\text{HCO}_3$ ,  $\text{H}_2\text{O}$ ; g) 1N NaOH, HOEt

Scheme XX provides a method for the preparation of 1,2,3,4-  
 10 tetrahydroisoquinoline compounds as exemplary fibrinogen receptor antagonists, as described in M. J. Fisher *et al.* (EP 0635492, Jan. 25, 1995). Accordingly, a 6-methoxy-3,4-dihydroisoquinoline, such as compound XX-1 is prepared by the method described by D. J. Sall and G. L. Grunewald (J. Med. Chem. 1987, 30,

- 2208-2216). The isoquinoline is treated with a haloacetic acid ester in the presence of a tertiary amine to afford the 2-acetic acid ester, as exemplified by compound XX-2. The 6-methoxy compound is converted into the corresponding 6-hydroxy compound by methods known in the art, for example with  $\text{BBr}_3$ , which is converted into the triflate with trifluorosulfonic acid anhydride. Palladium catalyzed carbonylation affords the 6-carboxy compound, such as compound XX-5, which is then condensed with an amine, as exemplified by (2-benzimidazolyl)acetic acid, employing a standard amide bond forming reagent to give the desired amide, such as compound XX-6. Saponification affords XX-7. Alternatively, the palladium catalyzed carbonylation reaction with the triflate, exemplified by compound XX-4, may be trapped with said aminomethyl compound to provide, after saponification, the corresponding 6-(2-benzimidazolyl)methylaminocarbonyl compound, XX-7.

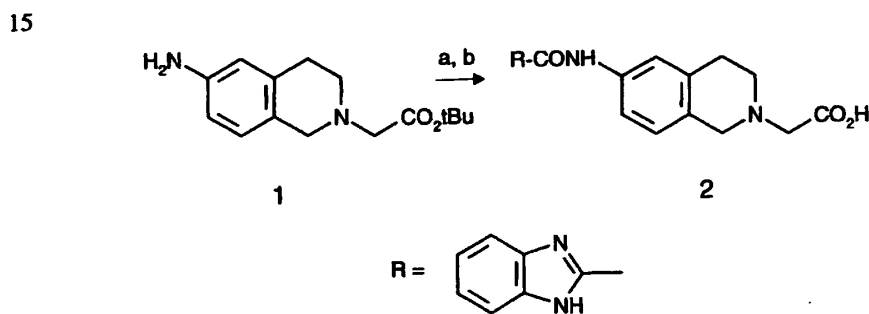
## Scheme XXI



- a) 1.  $\text{LiN}(\text{TMS})_2$ , 2.  $\text{ClCH}_2\text{CO}_2\text{Et}$ , DMF; b)  $\text{BBr}_3$ ; c)  $(\text{CF}_3\text{SO}_2)_2\text{O}$ ; d) CO,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , DIEA, NMP,  $\text{NH}_4\text{HCO}_3$ ,  $\text{H}_2\text{O}$ ; e)  $\text{H}_2\text{N-R}$ , EDC / HOBt, DIEA, DMF; f)  $\text{H}_2\text{N-R}$ , CO,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , DIEA, NMP,  $\text{NH}_4\text{HCO}_3$ ,  $\text{H}_2\text{O}$ ; g) 1N NaOH, HOEt

Scheme XXI provides a method for the preparation of 3,4-dihydroisoquinolin-1-one compounds as exemplary fibrinogen receptor antagonists, as described M. J. Fisher *et al.* (EP 0635492, Jan. 25, 1995). Accordingly, the 1-oxo compound **XXI-1**, prepared by the method described by D. J. Sall and G. L. Grunewald (J. Med. Chem. 1987, **30**, 2208-2216), is treated with a base, such as LiN(TMS)<sub>2</sub>, and a haloacetic acid ester to give a 2-acetic acid ester, as exemplified by compound **XXI-2**. The 1-oxo compound is then employed in the analogous series of reactions deployed in Scheme XX, substituting the corresponding 1-oxo analog, as shown in Scheme XXI, to provide **XXI-7**. As in Scheme XX, alternatively, the palladium catalyzed carbonylation reaction with the triflate, exemplified by compound **XXI-4**, may be trapped with an amine to provide, after saponification, the amide, **XXI-7**.

### Scheme XXII



a) RCO-X; b) TFA / CH<sub>2</sub>Cl<sub>2</sub>

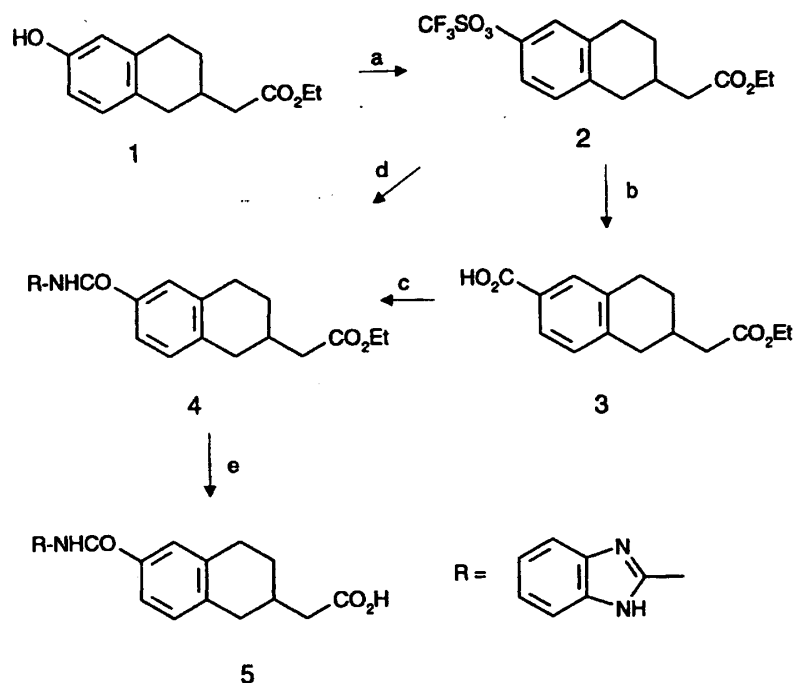
20 Scheme XXII provides a method for the preparation of 6-acylamino-tetraline compounds as exemplary fibrinogen receptor antagonists, as described M. J. Fisher *et al.* (EP 0635492, Jan. 25, 1995). Accordingly, a 6-amino-2-tert-butyl oxycarbonyl-tetral-1-one, exemplified by compound **XXII-1**, which is prepared according to the methods described in M. J. Fisher *et al.* (EP 0635492, Jan. 25,

25 1995), is condensed with an activated derivative of a carboxylic acid, such as the

activated derivative of (2-benzimidazolyl)acetic acid, to provide, after deesterification, the amide, **XXII-2**.

Scheme XXIII

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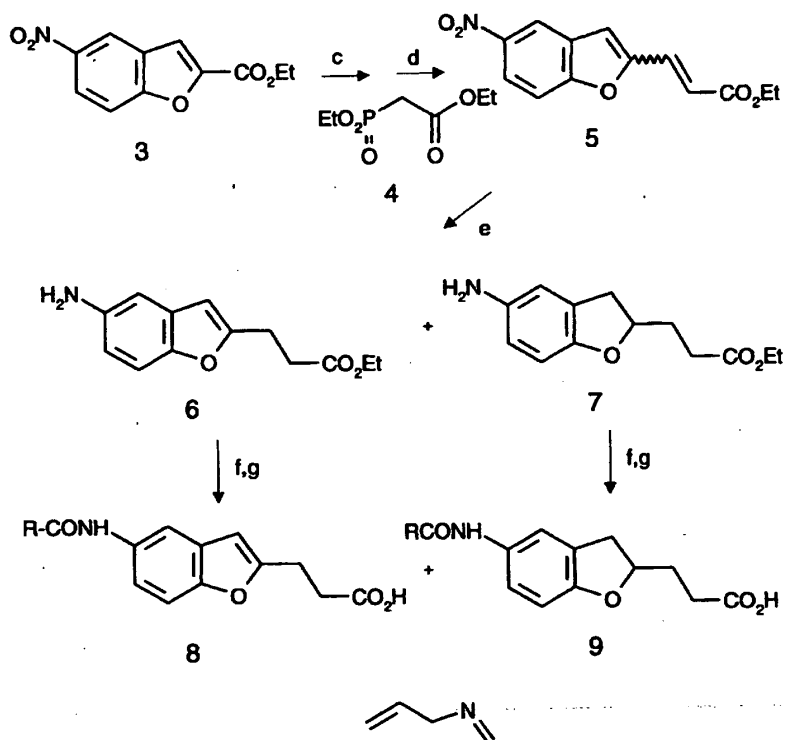
10 a)  $\text{CF}_3\text{SO}_2\text{O}$ ; b)  $\text{CO}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , DIEA, NMP,  $\text{NH}_4\text{HCO}_3$ ,  $\text{H}_2\text{O}$ ; c)  $\text{H}_2\text{N-R}$ , EDC /  $\text{HOBT}$ , DIEA, DMF; d)  $\text{H}_2\text{N-R}$ ,  $\text{CO}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , DIEA, NMP,  $\text{NH}_4\text{HCO}_3$ ,  $\text{H}_2\text{O}$ ; e) 1N NaOH, HOEt

Scheme XXIII provides a method for the preparation of 6-aminoacyltetraline compounds as exemplary fibrinogen receptor antagonists, as described M. J. Fisher *et al.* (EP 0635492, Jan. 25, 1995). Accordingly, an ethyloxycarbonylmethyl-6-hydroxy-tetral-1-one, exemplified by compound **XXIII-1**, which is prepared according to the methods described in M. J. Fisher *et al.* (EP 0635492, Jan. 25,

1995), is treated with triflic anhydride to provide the triflate, as exemplified by compound **XXIII -2**, which is employed in a palladium catalyzed carbonylation reaction to afford a carboxylic acid, such as compound **XXIII -3**, which is then condensed with an amine to provide, after deesterification, the 6-aminoacyl compound, **XXIII -5**. Alternatively, the palladium catalyzed carbonylation reaction with the triflate exemplified by compound **XXIII -2**, may be trapped with said amine compound to provide, after saponification, the corresponding 6-aminoacyl compound, **XXIII -5**.

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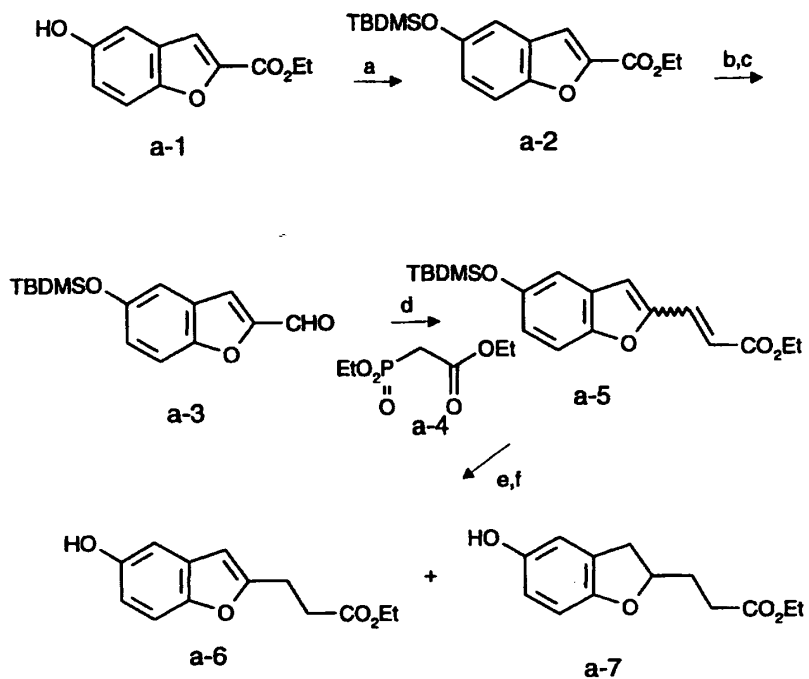
Scheme XXIV



- a)  $\text{BrCH}_2\text{CO}_2\text{Et}$ ,  $\text{K}_2\text{CO}_3$ , NaI; b) 1. DBU, EtOH, 2. HCl, EtOH; c) DiBAL,  $-78^\circ\text{C}$ ; d) NaH, THF; e)  $\text{H}_2$ , 10% Pd-C; f)  $\text{R}_2\text{CO-X}$ ; g) 1N NaOH, MeOH

Scheme XXIV provides a method for the preparation of 5-acylaminobenzofuran and 5-acylaminodihydrobenzofuran compounds as exemplary fibrinogen receptor antagonists, as described in M. L. Denney, *et al.* (EP 0655439, 31/5/95). Accordingly, a 4-nitrosalicylaldehyde, exemplified by compound XXIV-1, is treated with a haloacetic acid ester to give the phenoxyacetic acid ester, exemplified by compound XXIV -2. A 2-alkoxycarbonylfuran, exemplified by compound XXIV -3, is obtained by treating the aldehyde with base, for example with DBU. The 2-alkoxycarbonyl group is reduced to the aldehyde, for example with DiBAL. Wittig reaction affords the 2-acrylate ester, exemplified by compound XXIV -4, which is reduced to the benzofuran-2-propionic acid ester, exemplified by compound XXIV -5 and the dihydrobenzofuran-2-propionic acid ester, exemplified by compound XXIV -6. The amine XXIV -5 is then condensed with an activated derivative of a carboxylic acid to provide, after deesterification, the amide 5, XXIV -8. Alternatively, the amine XXIV -6 is condensed with an activated derivative of a carboxylic acid to provide, after deesterification, the amide, XXIV -7.

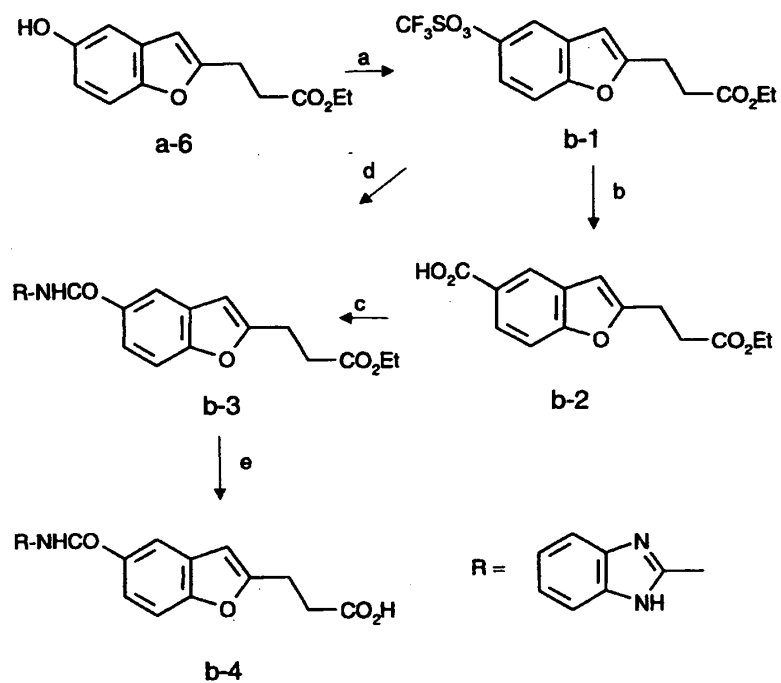
## Scheme XXVa



5

a) 1. TBDMS-Cl, imidazole; b) DiBAL-H, -78 °C; d) NaH, THF; e) H<sub>2</sub>, 5% Pd-C; f) Et<sub>3</sub>N+ F<sup>-</sup>

## Scheme XXVb

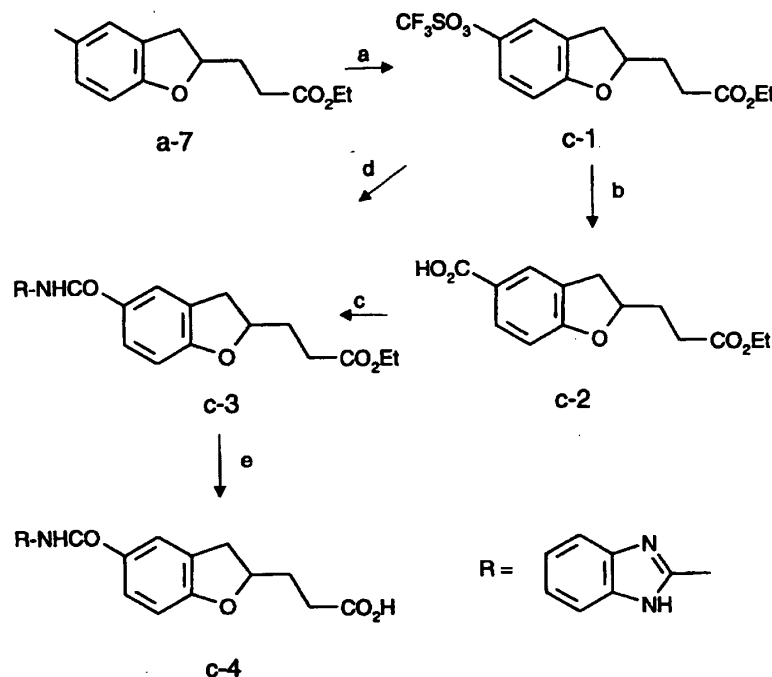


5

a)  $(CF_3SO_2)_2O$ ; b)  $CO$ ,  $Pd(OAc)_2$ ,  $PPh_3$ ,  $DIEA$ ,  $NMP$ ,  $NH_4HCO_3$ ,  $H_2O$ ; c)  $H_2N-R$ ,  $EDC$  /  $HOBt$ ,  $DIEA$ ,  $DMF$ ; d)  $H_2N-R$ ,  $CO$ ,  $Pd(OAc)_2$ ,  $PPh_3$ ,  $DIEA$ ,  $NMP$ ,  $NH_4HCO_3$ ,  $H_2O$  e)  $1N$   $NaOH$ ,  $EtOH$



Scheme XXVc



5

a)  $(\text{CF}_3\text{SO}_3)_2\text{O}$ ; b)  $\text{CO}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , DIEA, NMP,  $\text{NH}_4\text{HCO}_3$ ,  $\text{H}_2\text{O}$ ; c)  $\text{H}_2\text{N-R}$ , EDC / HOBt, DIEA, DMF; d)  $\text{H}_2\text{N-R}$ ,  $\text{CO}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , DIEA, NMP,  $\text{NH}_4\text{HCO}_3$ ,  $\text{H}_2\text{O}$  e) 1N NaOH, EtOH

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Scheme XXV provides a method for the preparation of 5-aminoacylbenzofuran and 5-aminoacyldihydrobenzofuran compounds as exemplary fibrinogen receptor antagonists, as described in M. L. Denney, *et al.* (EP 0655439, 31/5/95). Accordingly, a 5-hydroxybenzofuran-2-carboxylic acid ester, such as compound XXVa-1, prepared in the manner of M. L. Denney, *et al.* (EP 0655439, 31/5/95), is treated with TBDMS-Cl to provide the TBDMS derivative of the ester, XXVa-2. The ester is reduced to an aldehyde, such as compound XXVa-3. Wittig

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reaction affords the acrylic acid ester, XXVa-4. Catalytic reduction affords the benzofuran-2-acetic acid ester and the dihydrobenzofuran-2-acetic acid ester. Cleavage of the silyl ether group of each ester, by methods known to the art, affords either the benzofuran-2-acetic acid ester, XXVa-5, or the dihydrobenzofuran-2-acetic acid ester, XXVa-6.

As seen in Scheme XXVb and XXVc, each alcohol in turn may be converted to a carboxylic acid via palladium catalyzed carbonylation, such as compound XXVb-2 or XXVc-2, which is then condensed with an amine to provide, after deesterification, the amide XXVb-4 or XXVc-4. Alternatively, the palladium catalyzed carbonylation reaction with the triflate exemplified by compound XXVb-1, or XXVc-1, may be trapped with said aminomethyl compound to provide, after deesterification, the corresponding 6-aminoacyl compound, XXVb-4 or XXVc-4.

Amide coupling reagents as used herein denote reagents which may be used to form peptide bonds. Typical coupling methods employ carbodiimides, activated anhydrides and esters and acyl halides. Reagents such as EDC, DCC, DPPA, PPA, BOP reagent, HOBt, N-hydroxysuccinimide and oxalyl chloride are typical.

Coupling methods to form peptide bonds are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984, Ali *et al.* in *J. Med. Chem.*, 29, 984 (1986) and *J. Med. Chem.*, 30, 2291 (1987) are generally illustrative of the technique and are incorporated herein by reference.

Typically, the amine or aniline is coupled via its free amino group to an appropriate carboxylic acid substrate using a suitable carbodiimide coupling agent, such as N,N' dicyclohexyl carbodiimide (DCC), optionally in the presence of catalysts such as 1-hydroxybenzotriazole (HOBt) and dimethylamino pyridine (DMAP). Other methods, such as the formation of activated esters, anhydrides or acid halides, of the free carboxyl of a suitably protected acid substrate, and subsequent reaction with the free amine of a suitably protected amine, optionally in the presence of a base, are also suitable. For example, a protected Boc-amino acid or

Cbz-amidino benzoic acid is treated in an anhydrous solvent, such as methylene chloride or tetrahydrofuran(THF), in the presence of a base, such as N-methyl morpholine, DMAP or a trialkylamine, with isobutyl chloroformate to form the "activated anhydride", which is subsequently reacted with the free amine of a second  
5 protected amino acid or aniline.

The compounds of formula (XIX) and (XX) are commercially available or are prepared by methods known in the art such as illustrated herein disclosed in standard reference books, like the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (Wiley-Interscience). A generally applicable route to benzimidazoles is  
10 disclosed in Nestor et al, *J. Med. Chem.* **1984**, 27, 320. Representative methods for preparing compounds of formula (XX) are also common to the art and may be found, for instance, in EP-A 0 381 033.

Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as  
15 hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate  
20 organic amine. Cations such as  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ ,  $\text{Mg}^{++}$  and  $\text{NH}_4^+$  are specific examples of cations present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to formula (I)-(V) and (XXI)-(XXII) and a pharmaceutically acceptable carrier. Accordingly, the compounds of formula (I)-(V) and (XXI)-  
25 (XXII) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I)-(V) and (XXI)-(XXII) prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid  
30 formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or

buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds described herein are antagonists of the vitronectin receptor, and are useful for treating diseases wherein the underlying pathology is attributable to ligand or cell which interacts with the vitronectin receptor. For instance, these compounds are useful for the treatment of diseases wherein loss of the bone matrix creates pathology. Thus, the instant compounds are useful for the treatment of osteoporosis, hyperparathyroidism, Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastasis, bone loss due to immobilization or sex hormone deficiency. The compounds of this invention are also believed to have

utility as antitumor, anti-angiogenic, antiinflammatory and anti-metastatic agents, and be useful in the treatment of atherosclerosis and restenosis.

The compound is administered either orally or parenterally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption, or  
5 other such indication. The pharmaceutical composition containing the peptide is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg. For acute therapy, parenteral administration is preferred. An  
10 intravenous infusion of the peptide in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise level and method by which  
15 the compounds are administered is readily determined by one routinely skilled in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds may be tested in one of several biological assays to determine the concentration of compound which is required to have a given  
20 pharmacological effect.

#### **Inhibition of vitronectin binding**

*Solid-Phase [<sup>3</sup>H]-SK&F-107260 Binding to  $\alpha_v\beta_3$ :* Human placenta or human platelet  $\alpha_v\beta_3$  (0.1-0.3 mg/mL) in buffer T (containing 2 mM CaCl<sub>2</sub> and 1%  
25 octylglucoside) was diluted with buffer T containing 1 mM CaCl<sub>2</sub>, 1 mM MnCl<sub>2</sub>, 1 mM MgCl<sub>2</sub> (buffer A) and 0.05% NaN<sub>3</sub>, and then immediately added to 96-well ELISA plates (Corning, New York, NY) at 0.1 mL per well. 0.1 - 0.2  $\mu$ g of  $\alpha_v\beta_3$  was added per well. The plates were incubated overnight at 4°C. At the time of the experiment, the wells were washed once with buffer A and were incubated with  
30 0.1 mL of 3.5% bovine serum albumin in the same buffer for 1 hr at room

temperature. Following incubation the wells were aspirated completely and washed twice with 0.2 mL buffer A.

Compounds were dissolved in 100% DMSO to give a 2 mM stock solution, which was diluted with binding buffer (15 mM Tris-HCl (pH 7.4), 100 mM NaCl, 1 mM CaCl<sub>2</sub>, 1 mM MnCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>) to a final compound concentration of 100  $\mu$ M. This solution is then diluted to the required final compound concentration. Various concentrations of unlabeled antagonists (0.001 - 100  $\mu$ M) were added to the wells in triplicates, followed by the addition of 5.0 nM of [<sup>3</sup>H]-SK&F-107260 (65 - 86 Ci/mmol).

10 The plates were incubated for 1 hr at room temperature. Following incubation the wells were aspirated completely and washed once with 0.2 mL of ice cold buffer A in a well-to-well fashion. The receptors were solubilized with 0.1 mL of 1% SDS and the bound [<sup>3</sup>H]-SK&F-107260 was determined by liquid scintillation counting with the addition of 3 mL Ready Safe in a Beckman LS Liquid  
15 Scintillation Counter, with 40% efficiency. Nonspecific binding of [<sup>3</sup>H]-SK&F-107260 was determined in the presence of 2  $\mu$ M SK&F-107260 and was consistently less than 1% of total radioligand input. The IC<sub>50</sub> (concentration of the antagonist to inhibit 50% binding of [<sup>3</sup>H]-SK&F-107260) was determined by a nonlinear, least squares curve-fitting routine, which was modified from the LUNDON-2 program.  
20 The K<sub>i</sub> (dissociation constant of the antagonist) was calculated according to the equation:  $K_i = IC_{50} / (1 + L/K_d)$ , where L and K<sub>d</sub> were the concentration and the dissociation constant of [<sup>3</sup>H]-SK&F-107260, respectively.

Compounds of the present invention inhibit vitronectin binding to SK&F 107260 in the concentration range of about 0.001 to 50 micromolar.

25 Compounds of this invention are also tested for *in vitro* and *in vivo* bone resorption in assays standard in the art for evaluating inhibition of bone formation, such as the pit formation assay disclosed in EP 528 587, which may also be performed using human osteoclasts in place of rat osteoclasts, and the ovariectomized rat model, described by Wronski *et al.*, *Cells and Materials* 1991, Sup. 1, 69-74.

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**Vascular smooth muscle cell migration assay**

Rat or human aortic smooth muscle cells were used. The cell migration was monitored in a Transwell cell culture chamber by using a polycarbonate membrane with pores of 8  $\mu$ m (Costar). The lower surface of the filter was coated with vitronectin. Cells were suspended in DMEM supplemented with 0.2% bovine serum albumin at a concentration of  $2.5 - 5.0 \times 10^6$  cells/mL, and were pretreated with test compound at various concentrations for 20 min at 20°C. The solvent alone was used as control. 0.2 mL of the cell suspension was placed in the upper compartment of the chamber. The lower compartment contained 0.6 mL of DMEM supplemented with 0.2% bovine serum albumin. Incubation was carried out at 37°C in an atmosphere of 95% air/5% CO<sub>2</sub> for 24 hr. After incubation, the non-migrated cells on the upper surface of the filter were removed by gentle scraping. The filter was then fixed in methanol and stained with 10% Giemsa stain. Migration was measured either by a) counting the number of cells that had migrated to the lower surface of the filter or by b) extracting the stained cells with 10% acetic acid followed by determining the absorbance at 600 nM.

**PARATHYROIDECTOMIZED RAT MODEL**

Each experimental group consists of 5-6 male Sprague-Dawley rats. The rats are parathyroidectomized (by the vendor, Taconic Farms) 7 days prior to use. Twenty four hours prior to use, circulating ionized calcium levels are measured in whole blood immediately after it has been withdrawn by tail venipuncture into heparinized tubes. Rats are included if ionized Ca level (measured with a Ciba-Corning model 634 calcium pH analyzer) is  $\geq 1.2$  mM/L. The rats are then put on a diet of calcium-free chow and deionized water. At the start of the experiment the rats weigh approximately 100g. Baseline Ca levels are measured and the rats are administered control vehicle (saline) or compound (dissolved in saline) as a single intravenous (tail vein) bolus injection followed immediately by a single subcutaneous injection of either human parathyroid hormone 1-34 peptide (hPTH1-34, dose 0.2mg/kg in saline/0.1% bovine serum albumen, Bachem, Ca)

or the PTH vehicle. The calcemic response to PTH (and any effect of compound on this response) is measured 2h after compound/PTH administration.

#### **RAT ULNA DRIFT MODEL**

5

Each experimental group consists of 8-10 male Sprague-Dawley or Wistar rats of approximately 30-40g body weight at the start of the experiment. The agent being tested is administered by an appropriate route as single or multiple daily doses for a period of seven days. Prior to administration of the first dose, the rats are given a single dose of a  
10 fluorescent marker (tetracycline 25mg/kg, or calcein 10mg/kg) that labels the position of bone forming surfaces at that point in time. After dosing of compound has been completed, the rats are killed and both forelimbs are removed at the elbow, the foot is removed at the ankle and the skin removed. The sample is frozen and mounted vertically on a microtome chuck. Cross sections of the midshaft region of the ulna are cut in the  
15 cryostat. The rate of bone resorption is measured morphometrically in the medial-dorsal portion of the cortical bone. The measurement is done as follows: the amount of bone resorbed at the periosteal surface is equal to the distance by which the periosteal surface has advanced towards the fluorescent label which had been incorporated at the endosteal bone formation surface on day zero; this distance is calculated by subtracting the width of  
20 bone between the label and the periosteal surface on day 7 from the width on day zero; the resorption rate in microns per day is calculated by dividing the result by 7.

#### **HUMAN OSTEOCLAST RESORPTION ASSAY ("PIT ASSAY")**

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- Aliquots of osteoclastoma-derived cell suspensions are removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000rpm, 5 mins at 4°C).

30

- Aspirate the medium and replace it with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium. Incubate for 30 mins on ice and mix the cell suspension frequently.



- The cells are washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 mins at 4°C) and the cells are transferred to a sterile 15 ml centrifuge tube. The number of mononuclear cells are enumerated in an improved Neubauer counting chamber.
- 5
- Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, are removed from their stock bottle and placed into 5 ml of fresh medium (this washes away the toxic azide preservative). The medium is removed by immobilizing the beads on a magnet and is replaced with fresh medium.
- 10
- The beads are mixed with the cells and the suspension is incubated for 30 mins on ice. The suspension is mixed frequently.
- 15
- The bead-coated cells are immobilized on a magnet and the remaining cells (osteoclast-rich fraction) are decanted into a sterile 50 ml centrifuge tube.
- Fresh medium is added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process is repeated x10. The bead-coated cells are discarded.
- 20
- The osteoclasts are enumerated in a counting chamber, using a large-bore disposable plastic pasteur to charge the chamber with the sample.
- 25
- The cells are pelleted by centrifugation and the density of osteoclasts adjusted to  $1.5 \times 10^4$ /ml in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate.
- 3ml aliquots of the cell suspension ( per treatment) are decanted into 15ml centrifuge tubes. The cells are pelleted by centrifugation.
- 30
- To each tube 3ml of the appropriate treatment are added (diluted to 50 uM in the EMEM medium). Also included are appropriate vehicle controls, a positive control

(87MEM1 diluted to 100 ug/ml) and an isotype control (IgG2a diluted to 100 ug/ml). Incubate at 37°C for 30 mins.

- 5      • 0.5ml aliquots of the cells are seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 hours. Each treatment is screened in quadruplicate.
- The slices are washed in six changes of warm PBS (10 ml / well in a 6-well plate) and then placed into fresh treatment or control. Incubate at 37°C for 48 hours.
- 10    **Tartrate resistant acid phosphatase (TRAP) procedure** (selective stain for cells of the osteoclast lineage).
- The slices are washed in phosphate buffered saline and fixed in 2% gluteraldehyde (in 0.2M sodium cacodylate) for 5 mins.
- 15    • They are washed in water and incubated in TRAP buffer for 5 mins at 37°C.
- Following a wash in cold water they are incubated in cold acetate buffer / fast red garnet for 5 mins at 4°C.
- 20    • Excess buffer is aspirated, and the slices are air dried following a wash in water.
- The TRAP positive osteoclasts are enumerated by bright-field microscopy and are then removed from the surface of the dentine by sonication.
- 25    • Pit volumes are determined using the Nikon/Lasertec ILM21W confocal microscope.

#### **Human osteoclast resorption and adhesion assays**

- 30    Pit resorption and adhesion assays have been developed and standardized using normal human osteoclasts derived from osteoclastoma tissue. The osteoclast

- population is negatively selected from the osteoclastoma cell suspensions using magnetic beads (Dynal Inc, NY). These beads are coated with a murine monoclonal antibody that recognizes a human class II major histocompatibility antigen that is present on a large number of mononuclear cells in the cell suspensions. The cells
- 5 that express this antigen, and consequently bind the beads, are removed from the mixture of cells using a magnet. The osteoclast-rich suspension is then ready to use in the assays detailed below.

**Resorption assay (with ELISA readout)**

- 10 Enriched preparations of osteoclasts are preincubated for 30 minutes at 37°C with test compound (4 doses) or controls. They are then seeded onto bovine cortical bone slices in wells of a 48-well tissue culture plate and are incubated for a further 2 hours at 37°C. The bone slices are washed in six changes of warm phosphate buffered saline (PBS), to remove non-adherent cells, and are then returned to wells of a 48
- 15 well plate containing fresh compound or controls. The tissue culture plate is then incubated for 48 hours at 37°C. The supernatants from each well are aspirated into individual tubes and are screened in a competitive ELISA that detects a collagen peptide that is released during the resorption process. This is a commercially available ELISA (Osteometer, Denmark) that contains a rabbit antibody that
- 20 specifically reacts with an 8-amino acid sequence (Glu-Lys-Ala-His- Asp-Gly-Gly-Arg) that is present in the carboxy-terminal telopeptide of the  $\alpha$ 1-chain of type I collagen. The results are expressed as % inhibition of resorption compared to a vehicle control.

**25 Adhesion assay**

- Osteoclastoma-derived osteoclasts are preincubated with compound (4 doses) or controls at 37°C for 30 minutes. The cells are then seeded onto osteopontin-coated slides (human or rat osteopontin, 2.5ug/ml) and incubated for 2 hours at 37°C. Non adherent cells are removed by washing the slides vigorously in PBS and the cells
- 30 remaining on the slides are fixed in acetone. The osteoclasts are stained for tartrate-resistant acid phosphatase (TRAP), a selective marker for cells of this phenotype, and are enumerated by light microscopy. The results are expressed as % inhibition of adhesion compared to a vehicle control.

Inhibition of RGD-mediated GPIIb-IIIa binding**Purification of GPIIb-IIIa**

Ten units of outdated, washed human platelets (obtained from Red Cross) were lysed by gentle stirring in 3% octylglucoside, 20 mM Tris-HCl, pH 7.4, 140 mM NaCl, 2 mM CaCl<sub>2</sub> at 4°C for 2 h. The lysate was centrifuged at 100,000g for 1 h. The supernatant obtained was applied to a 5 mL lentil lectin sepharose 4B column (E.Y. Labs) preequilibrated with 20 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM CaCl<sub>2</sub>, 1% octylglucoside (buffer A). After 2 h incubation, the column was washed with 50 mL cold buffer A. The lectin-retained GPIIb-IIIa was eluted with buffer A containing 10% dextrose. All procedures were performed at 4°C. The GPIIb-IIIa obtained was >95% pure as shown by SDS polyacrylamide gel electrophoresis.

**15 Incorporation of GPIIb-IIIa in Liposomes.**

A mixture of phosphatidylserine (70%) and phosphatidylcholine (30%) (Avanti Polar Lipids) were dried to the walls of a glass tube under a stream of nitrogen. Purified GPIIb-IIIa was diluted to a final concentration of 0.5 mg/mL and mixed with the phospholipids in a protein:phospholipid ratio of 1:3 (w:w). The mixture was resuspended and sonicated in a bath sonicator for 5 min. The mixture was then dialyzed overnight using 12,000-14,000 molecular weight cutoff dialysis tubing against a 1000-fold excess of 50 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM CaCl<sub>2</sub> (with 2 changes). The GPIIb-IIIa-containing liposomes were centrifuged at 12,000g for 15 min and resuspended in the dialysis buffer at a final protein concentration of approximately 1 mg/mL. The liposomes were stored at -70°C until needed.

**Competitive Binding to GPIIb-IIIa**

The binding to the fibrinogen receptor (GPIIb-IIIa) was assayed by an indirect competitive binding method using [<sup>3</sup>H]-SK&F-107260 as an RGD-type ligand. The binding assay was performed in a 96-well filtration plate assembly (Millipore Corporation, Bedford, MA) using 0.22 µm hydrophilic durapore membranes. The wells were precoated with 0.2 mL of 10 µg/mL polylysine (Sigma Chemical Co., St. Louis, MO.) at room temperature for 1 h to block nonspecific binding. Various concentrations of unlabeled benzodiazapines were added to the

wells in quadruplicate. [<sup>3</sup>H]-SK&F-107260 was applied to each well at a final concentration of 4.5 nM, followed by the addition of 1 µg of the purified platelet GPIIb-IIIa-containing liposomes. The mixtures were incubated for 1 h at room temperature. The GPIIb-IIIa-bound [<sup>3</sup>H]-SK&F-107260 was separated from the unbound by filtration using a Millipore filtration manifold, followed by washing with ice-cold buffer (2 times, each 0.2 mL). Bound radioactivity remaining on the filters was counted in 1.5 mL Ready Solve (Beckman Instruments, Fullerton, CA) in a Beckman Liquid Scintillation Counter (Model LS6800), with 40% efficiency. Nonspecific binding was determined in the presence of 2 µM unlabeled SK&F-107260 and was consistently less than 0.14% of the total radioactivity added to the samples. All data points are the mean of quadruplicate determinations.

Competition binding data were analyzed by a nonlinear least-squares curve fitting procedure. This method provides the IC<sub>50</sub> of the antagonists (concentration of the antagonist which inhibits specific binding of [<sup>3</sup>H]-SK&F-107260 by 50% at equilibrium). The IC<sub>50</sub> is related to the equilibrium dissociation constant (K<sub>i</sub>) of the antagonist based on the Cheng and Prusoff equation:  $K_i = IC_{50}/(1+L/K_d)$ , where L is the concentration of [<sup>3</sup>H]-SK&F-107260 used in the competitive binding assay (4.5 nM), and K<sub>d</sub> is the dissociation constant of [<sup>3</sup>H]-SK&F-107260 which is 4.5 nM as determined by Scatchard analysis

Compounds of the present invention inhibit the vitronectin binding to SK&F 007260 with a K<sub>i</sub> at the vitronectin receptor that is about ten-fold greater than that for the fibrinogen receptor. Preferred compounds have a K<sub>i</sub> at the vitronectin receptor that is thirty-fold greater than that at the fibrinogen receptor. The most preferred compounds have a K<sub>i</sub> at the vitronectin receptor that is a hundred-fold greater than that at the fibrinogen receptor.

The examples which follow are intended in no way to limit the scope of this invention, but are provided to illustrate how to make and use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

### General

5 Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer.  $\text{CDCl}_3$  is deuteriochloroform,  $\text{DMSO-d}_6$  is hexadeuteriodimethylsulfoxide, and  $\text{CD}_3\text{OD}$  is tetradeuteriomethanol. Chemical shifts are reported in parts per million ( $\delta$ ) downfield from the internal standard tetramethylsilane. Abbreviations for NMR  
10 data are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets, app=apparent, br=broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared  
15 spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers ( $\text{cm}^{-1}$ ). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were  
20 taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical and  
25 preparative HPLC were carried out on Rainin or Beckman chromatographs. ODS refers to an octadecylsilyl derivatized silica gel chromatographic support. 5  $\mu$  Apex-ODS indicates an octadecylsilyl derivatized silica gel chromatographic support having a nominal particle size of 5  $\mu$ , made by Jones Chromatography, Littleton, Colorado. YMC ODS-AQ® is an ODS chromatographic support and is a registered  
30 trademark of YMC Co. Ltd., Kyoto, Japan. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic support, and is a registered trademark of Hamilton Co., Reno, Nevada) Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado.

Methyl ( $\pm$ )-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-  
35 benzodiazepine-2-acetate, methyl (2S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (2R)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl ( $\pm$ )-7-carboxy-4-

isopropyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-7-carboxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-8-carboxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, methyl (±)-7-amino-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid, and tert-butyl 4-fluoro-3-methylbenzoate were prepared by the method of Bondinell, et al., WO 93/00095. Methyl (±)-7-carboxy-4-(2-methoxyethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-7-carboxy-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-7-carboxy-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate, (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, 2-(methylaminomethyl)benzimidazole dihydrochloride, and 4-aza-5-methyl-2-(methylamino)methylbenzimidazole were prepared according to P50256-1.

### Preparation 1

#### Preparation of 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride

20

##### a) 2,3-Diamino-6-methylpyridine

10% Pd/C (3.2 g, 3 mmole) was added to a solution of 2-Amino-6-methyl-3-nitropyridine (2.30 g, 15 mmole) in absolute EtOH (150 mL), and the mixture was shaken at RT under H<sub>2</sub> (50 psi). After 1.5 hr, the mixture was filtered through celite®, and the filtrate was concentrated under vacuum to afford the title compound as a yellow oil. This was used without further purification: <sup>1</sup>H NMR (250 MHz, CD<sub>3</sub>OD) δ 6.82 (d, 1H), 6.36 (d, 1H), 2.25 (s, 3H).

25

##### b) 2-Amino-3-[(benzyloxycarbonyl)glycyl]amino-6-methylpyridine

30

DCC (3.09 g, 15 mmole) was added to a solution of 2,3-diamino-6-methylpyridine (15 mmole) and Cbz-glycine (3.14 g, 15 mmole) in DMF (19 mL) and CH<sub>2</sub>Cl<sub>2</sub> (19 mL) at 0°C under argon. When the DCC had dissolved, the slightly cloudy solution was warmed to RT. After 18.5 hr, the mixture was filtered through celite®, and the filtrate was concentrated to dryness on the rotavap. The residue was reconcentrated from xylenes (to remove DMF) to leave a yellow solid. Silica gel chromatography (10% MeOH/CHCl<sub>3</sub>) gave the title compound (2.24 g, 48%) as a yellow solid: TLC R<sub>f</sub> (10% MeOH/CHCl<sub>3</sub>) 0.57; <sup>1</sup>H NMR (250 MHz, DMSO - d<sub>6</sub>) δ

35

9.11 (br s, 1 H), 7.48 - 7.60 (br t, 1 H), 7.20 - 7.48 (m, 6 H), 6.40 (d, 1 H), 5.69 (br s, 2 H), 5.06 (s, 2 H), 3.82 (d, 2 H), 2.23 (s, 3 H).

c) 4-Aza-2-(benzyloxycarbonyl)aminomethyl-5-methylbenzimidazole

- 5 A solution of 2-amino-3-[(benzyloxycarbonyl)glycyl]amino-6-methylpyridine (2.24 g, 7.13 mmole) in glacial AcOH (70 mL) was heated to reflux under argon. After 17 hr, the solution was concentrated (rotavap, high vacuum), and the residue was reconcentrated from toluene (to remove AcOH). The resulting yellow oil was treated with hot EtOAc (20 mL) and the mixture was cooled to RT.
- 10 The solid was collected by suction filtration and washed with EtOAc to afford the title compound (1.72 g, 81%) as an off-white solid: -TLC R<sub>f</sub> (15% MeOH/CHCl<sub>3</sub>) 0.63; MS (ES) m/e 297.4 (M + H)<sup>+</sup>.

d) 2-(Aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride

- 15 10% Pd/C (153 mg, 0.14 mmole) was added to a solution of 4-aza-2-(benzyloxycarbonyl)aminomethyl-5-methylbenzimidazole (213.4 mg, 0.72 mmole) and 1.0 N HCl (1.44 mL, 1.44 mmole) in absolute EtOH (7.2 mL). The mixture was purged with H<sub>2</sub>, then was stirred briskly at RT under H<sub>2</sub> (balloon). After 2 hr, the reaction was filtered through celite, and the filtrate was concentrated on the rotavap
- 20 to leave the title compound as an off-white solid: MS (ES) m/e 163.2 (M + H)<sup>+</sup>.

Preparation 2

- 25 Preparation of methyl (±)-2,3,4,5-tetrahydro-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

a) tert-Butyl 3-[(3,3-dimethylbutyl)amino]methyl-4-nitrobenzoate

- A mixture of tert-butyl 3-methyl-4-nitrobenzoate (WO 93/00095; 17.7 g, 74.7 mmol), NBS (19.9 g, 112.0 mmol), benzoyl peroxide (1.81 g, 7.47 mmol), and
- 30 CCl<sub>4</sub> (370 mL) was heated at reflux. After 17.5 h, the reaction was cooled thoroughly in ice and filtered to remove the precipitated succinimide. The filtrate was concentrated to leave a brownish-yellow oil.

- This oil (4.2 g, 13.29 mmol), was dissolved in dry THF (50 mL), and 3,3-dimethylbutylamine (3.0 g, 29.64 mmol) was added all at once. The orangish-
- 35 yellow solution was stirred at RT for 80 min, then was concentrated to remove the THF. The residue was diluted with Et<sub>2</sub>O (150 mL) and washed sequentially with 1.0 N NaOH (25 mL) and H<sub>2</sub>O (25 mL). The combined aqueous layers were back-



extracted with Et<sub>2</sub>O (50 mL), and the combined organic layers were washed with brine (25 mL) and dried (MgSO<sub>4</sub>). Concentration gave the crude title compound (4.19 g, 94%) as a light-brown oil: MS (ES) m/e 337.2 (M+H)<sup>+</sup>.

- 5    b) tert-Butyl 3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methyl-4-nitrobenzoate

Di-tert-butyl dicarbonate (4.0 g, 18.39 mmol) was added all at once to a solution of tert-butyl 3-[(3,3-dimethylbutyl)amino]methyl-4-nitrobenzoate (4.12 g, 12.26 mmol) in CHCl<sub>3</sub> (80 mL) at RT. After 18 h, the reaction was concentrated and reconcentrated from hexanes (to remove CHCl<sub>3</sub>). Silica gel chromatography (10-25% EtOAc/hexanes) gave the title compound (5.0 g, 93%) as a yellow oil: MS (ES) m/e 437.2 (M+H)<sup>+</sup>, 459.2 (M+Na)<sup>+</sup>.

- 15    c) tert-Butyl 4-amino-3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methyl benzoate

10% Pd/C (1.0 g, 0.94 mmol) was added to a solution of tert-butyl 3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methyl-4-nitrobenzoate (4.95 g, 11.35 mmol) in EtOAc (50 mL), and the mixture was shaken on a Parr apparatus at RT under H<sub>2</sub> (55 psi). After 4 h, the reaction was filtered through celite®, and the filtrate was concentrated to afford the title compound (4.3 g, 93%) as a reddish-brown oil: MS (ES) m/e 407.4 (M+H)<sup>+</sup>.

- 25    d) tert-Butyl (±)-4-[2-(1,4-dimethoxy-1,4-dioxobutyl)amino]-3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate

A solution of tert-butyl 4-amino-3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate (5.6 g, 13.79 mmol) and dimethylacetylene dicarboxylate (1.86 mL, 15.17 mmol) in MeOH (28 mL) was heated at reflux for 1 h, then was cooled to RT. The resulting solution was combined with MeOH (80 mL) and 10% Pd/C (2.9 g, 2.76 mmol), and the mixture was shaken on a Parr apparatus at RT under H<sub>2</sub> (50 psi). After 22 h, the reaction was filtered through celite®, and the filtrate was concentrated on the rotavap. The residue was reconcentrated from CHCl<sub>3</sub> (to remove MeOH), then was chromatographed on silica gel (25% EtOAc/hexanes). The title compound (2.64 g, 42%) was obtained as a faintly yellow oil: MS (ES) m/e 551.2 (M+H)<sup>+</sup>.

35

- e) Methyl (±)-2,3,4,5-tetrahydro-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

TFA (25 mL) was added all at once to a solution of tert-butyl ( $\pm$ )-4-[2-(1,4-dimethoxy-1,4-dioxobutyl)amino]-3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate (12.64 g, 4.8 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (25 mL) at  $0^\circ\text{C}$ , and the faintly yellow solution was warmed to RT. After 1 h, the solution was concentrated on the rotavap, and the residue was reconcentrated from toluene (to remove residual TFA). The resulting oil was combined with toluene (50 mL) and  $\text{Et}_3\text{N}$  (3.34 mL, 24 mmol), and the mixture was heated to reflux. A light yellow, homogeneous solution was produced. After 16 h, the reaction was concentrated on the rotavap to leave a solid residue. This was dissolved in a minimum of MeOH (ca. 10 mL), diluted with  $\text{H}_2\text{O}$  (10 mL), and acidified with glacial AcOH to pH 4.5. The mixture was filtered, and the precipitate was washed sequentially with MeOH and  $\text{Et}_2\text{O}$ , then was dried in high vacuum to afford the title compound (1.88 g, 93%) as a nearly colorless powder: MS (ES) m/e 363.2 ( $\text{M}+\text{H}$ ) $^+$ .

### Preparation 3

#### Preparation of Bis[(benzimidazol-2-yl)methyl]amine tris(trifluoroacetate)

a) Bis[[1-N-(tert-butoxycarbonyl)benzimidazol-2-yl)methyl]-N-(tert-butoxycarbonyl)amine

To a stirred solution of 2-aminomethylbenzimidazole dihydrochloride hydrate (6.26 g, 28.4 mmol) and triethylamine (4.0 mL, 28.4 mmol) in dry THF (50 mL) was added 1-(tert-butoxycarbonyl)-2-(bromomethyl)benzimidazole (P50256-1; 2.00 g, 9.48 mmol) in THF (30 mL). After 8 h, a solution of di-tert-butyl dicarbonate (10.0 g, 45.84 mmol) in  $\text{CHCl}_3$  (50 mL) was added slowly. The resulting mixture was stirred at RT overnight then was concentrated. The residue was taken up in  $\text{CH}_2\text{Cl}_2$  (150 mL), and washed sequentially with water (60 mL), 5%  $\text{NaHCO}_3$  (60 mL), and brine (60 mL). Drying ( $\text{MgSO}_4$ ), concentration, and silica gel chromatography (6% MeOH/ $\text{CH}_2\text{Cl}_2$ ) gave the title compound (0.46 g, 8%) as a faint yellow oil: MS (ES) m/e 578.4 ( $\text{M}+\text{H}$ ) $^+$ .

b) Bis[(benzimidazol-2-yl)methyl]amine tris(trifluoroacetate)

A solution of TFA (3 mL) and  $\text{CH}_2\text{Cl}_2$  (9 mL) at RT was added all at once to bis[[1-N-(tert-butoxycarbonyl)benzimidazol-2-yl)methyl]-N-(tert-butoxycarbonyl)amine (0.23 g, 0.4 mmol). After 35 min, the solution was concentrated on the rotavap, and the residue was reconcentrated from toluene (to

remove residual TFA) to afford the title compound (0.17 g, 68%) as an off-white powder: MS (ES) m/e 278.0 (M+H)<sup>+</sup>.

#### Preparation 4

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##### Preparation of 2-[[1-[(benzimidazol-2-yl)methyl]benzimidazole]methyl]amine bis(trifluoroacetate)

10 a) [[1-N-(tert-Butoxycarbonyl)benzimidazol-2-yl)methyl]-N-(tert-butoxycarbonyl)amine

To a stirred solution of 2-aminomethylbenzimidazole dihydrochloride hydrate (3.0 g, 13.63 mmol) and triethylamine (8.44 mL, 61.3 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) a solution of di-tert-butyl dicarbonate (6.54 g, 30.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added at 0°C. The reaction was stirred at RT for 1 h, then more of triethylamine (1.9 mL, 13.8 mmol) and di-tert-butyl dicarbonate (2.97 g, 13.63 mmol) were added. The resulting mixture was stirred at RT for 24 h, then was concentrated. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed sequentially with 0.5 N HCl (2x40 mL), 5% NaHCO<sub>3</sub> (50 mL), and brine (50 mL). The crude product was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/ether to give the title compound (2.8 g, 59%) as a white powder: MS (ES) m/e 348.2 (M+H)<sup>+</sup>.

25 b) 2-[[1-[[1-(tert-Butoxycarbonyl)benzimidazol-2-yl)methyl]benzimidazole]methyl]-N,N-di-(tert-butoxycarbonyl)amine

To a stirred solution of [[1-N-(tert-butoxycarbonyl)benzimidazol-2-yl)methyl]-N-(di-tert-butoxycarbonyl)amine (0.6 g, 1.73 mmol) and NaH (0.1 g, 4.17 mmol) in dry THF (12 mL) and DMF (4 mL) was added 1-(tert-butoxycarbonyl)-2-(bromomethyl)benzimidazole (0.6 g, 1.93 mmol). The resulting mixture was stirred at RT for 1 h, then was concentrated. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and washed sequentially with water (50 mL), 5% NaHCO<sub>3</sub> (30 mL), and brine (30 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (2:3 EtOAc/hexanes) gave the title compound (0.27 g, 27%) as a faint yellow oil: MS (ES) m/e 578.2 (M+H)<sup>+</sup>.

35 c) 2-[[1-[(Benzimidazol-2-yl)methyl]benzimidazole]methyl]amine bis(trifluoroacetate)

A solution of TFA/CH<sub>2</sub>Cl<sub>2</sub> (30 mL, 25%) at RT was added all at once to 2-[[1-[[1-N-tert-butoxycarbonyl)benzimidazol-2-yl)methyl]benzimidazole]methyl]-N,N-

di-(tert-butoxycarbonyl)amine (0.25 g, 0.43 mmol). After 25 min, the solution was concentrated on the rotavap, and the crude product was recrystallized from  $\text{CH}_2\text{Cl}_2/\text{ether}$  to give the title compound (0.17 g, 63%) as an off-white powder. MS (ES) m/e 278.0 (M+H)<sup>+</sup>.

5

### Example 1

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

10

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

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EDC (138 mg, 0.72 mmole) was added to a solution of methyl (±)-7-carboxy-4-(2-methoxyethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (202 mg, 0.60 mmole), 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride (0.72 mmole), HOBt · H<sub>2</sub>O (97 mg, 0.72 mmole), and diisopropylethylamine (0.84 mL, 4.8 mmole) in anhydrous  $\text{CH}_3\text{CN}$  (3 mL) at RT. After 16 hr, the reaction was concentrated, and the residue was reconcentrated from xylenes/ $\text{CHCl}_3$ . Silica gel chromatography (15% MeOH/ $\text{CHCl}_3$ ) gave the title compound (impure): TLC R<sub>f</sub> (15% MeOH/ $\text{CHCl}_3$ ) 0.55; MS (ES) m/e 481.5 (M + H)<sup>+</sup>. This was used without further purification.

20

b) (±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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A two-phase mixture of methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.60 mmole), 1.0 N LiOH (1.8 mL, 1.8 mmole), and THF (4.2 mL) was stirred at RT for 45 min, then was concentrated to remove the THF. The aqueous layer was washed with Et<sub>2</sub>O (2 x 2 mL), and the Et<sub>2</sub>O layers were discarded. The aqueous layer was diluted with  $\text{CH}_3\text{CN}$  (2 mL) and acidified with TFA (0.23 mL). The resulting solution was concentrated to dryness on the rotavap, and the residue was purified by ODS chromatography (12%  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  containing 0.1% TFA (250 mL), then 15%  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  containing 0.1% TFA). Concentration and lyophilization gave the title compound (199.5 mg, 50% for two steps) as a light

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yellow powder: HPLC (PRP-1®, 15% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) K' = 1.4; MS (ES) m/e 467 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub> · 1.5 CF<sub>3</sub>CO<sub>2</sub>H · 1.33 H<sub>2</sub>O: C, 47.21; H, 4.60; N, 12.70. Found: C, 47.20; H, 4.73; N, 12.79.

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### Example 2

#### Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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##### a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

EDC (230 mg, 1.2 mmole) was added to a solution of methyl (±)-7-carboxy-4-(2-methoxyethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (336.4 mg, 1.0 mmole), 2-(aminomethyl)benzimidazole dihydrochloride hydrate (264 mg, 1.2 mmole), HOBt · H<sub>2</sub>O (162 mg, 1.2 mmole), and diisopropylethylamine (0.70 mL, 4.0 mmole) in anhydrous DMF (5 mL) at RT. After 17 hr, the reaction was concentrated, and the residue was reconcentrated from xylenes (2 x) to remove DMF. The residue was diluted with H<sub>2</sub>O (3 mL) and extracted with CHCl<sub>3</sub> (3 x 5 mL). The combined extracts were treated with MeOH (2 mL) to dissolve a precipitate, then were dried (MgSO<sub>4</sub>) and concentrated. Reconcentration from xylenes (to remove residual DMF) left a light yellow solid. This was dissolved in MeOH/CHCl<sub>3</sub>, and the solution was concentrated to leave an oil. Silica gel chromatography (10% MeOH/CHCl<sub>3</sub>) gave an off-white solid, which was triturated with EtOAc (3 mL) to afford the title compound (397.1 mg, 85%) as a colorless solid: TLC R<sub>f</sub> (10% MeOH/CHCl<sub>3</sub>) 0.46; MS (ES) m/e 466.2 (M + H)<sup>+</sup>.

##### b) (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N LiOH (1.0 mL, 1.0 mmole) was added to a suspension of methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (397 mg, 0.85 mmole) in THF (4.3 mL) and H<sub>2</sub>O (3.3 mL) at RT. The light yellow mixture was stirred at 40 °C for 1 hr, and the resulting homogeneous solution was then stirred at RT for 17.5 hr. The reaction was concentrated, and the resulting oil was dissolved in H<sub>2</sub>O (4 mL). The solution was filtered to remove particulates, and the filtrate was

neutralized with 1.0 N HCl (1.0 mL). The yellowish solid was collected and triturated with good stirring with hot 1:1 CH<sub>3</sub>CN/H<sub>2</sub>O. The resulting solid was collected, washed with plenty of 1:1 CH<sub>3</sub>CN/H<sub>2</sub>O, and dried in high vacuum (40°C) to afford the title compound (327.9 mg, 85%) as a colorless powder. HPLC (PRP-1®, 15% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) K' = 4.6; MS (ES) m/e 452.2 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>: C, 61.19; H, 5.58; N, 15.51. Found: C, 61.18; H, 5.58; N, 15.39.

### Example 3

#### Preparation of (±)-4-[4-[[[1H-benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoic acid

##### a) Ethyl 3-hydroxy-4-(4-methoxyphenyl)-3-phenylbutanoate

Anhydrous EtOAc (4.3 mL, 44 mmole) was added dropwise over 5 - 6 min to a solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 40 mL, 40 mmole) in dry THF (60 mL) in a flame-dried flask at -78°C under argon. The yellow solution was stirred at -78°C for 0.5 hr, then a solution of 2-(4-methoxyphenyl)-1-phenylethanone (*Chem. Ber.* 1958, 91, 755-759; 4.53 g, 20 mmole) in dry THF (20 mL) was added dropwise over 12 min. Additional THF (2 mL) was used in transfer. After 0.5 hr, The reaction was quenched with satd NH<sub>4</sub>Cl (120 mL) and warmed to RT. EtOAc extraction, drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (20% EtOAc/hexanes) gave the title compound (6.13 g, 96%) as a light yellow oil: TLC R<sub>f</sub> (20% EtOAc/hexanes) 0.34; MS (ES) m/e 315.2 (M + H)<sup>+</sup>.

##### b) Ethyl 4-(4-methoxyphenyl)-3-phenylbutanoate

Boron trifluoride etherate (4.8 mL, 39 mmole) was added dropwise over 3 min to a solution of ethyl 3-hydroxy-4-(4-methoxyphenyl)-3-phenylbutanoate (6.13 g, 19.5 mmole) and triethylsilane (6.2 mL, 39 mmole) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (49 mL) at 0°C under argon. The reaction was stirred at RT overnight, then was quenched with 5% NaHCO<sub>3</sub> (100 mL). The mixture was stirred briskly for 10 min, then was separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was reconcentrated from hexanes (to remove CH<sub>2</sub>Cl<sub>2</sub>) to leave a yellow oil. This was dissolved in absolute EtOH (100 mL), and 10% Pd/C (775 mg, 1.95 mmole) was added. The mixture was shaken on a Parr apparatus at RT under H<sub>2</sub> (50 psi) for 2 hr, then was filtered through celite®. The filtrate was concentrated, and the residue was

chromatographed on silica gel (15 % EtOAc/hexanes). The title compound (5.27 g, 91%) was obtained as a colorless oil: TLC  $R_f$  (15% EtOAc/hexanes) 0.40; MS (ES)  $m/e$  299.2 (M + H)<sup>+</sup>.

5 c) Ethyl 4-(4-hydroxyphenyl)-3-phenylbutanoate

Anhydrous aluminum trichloride (4.49 g, 33.7 mmole) was added all at once to solution of ethyl 4-(4-methoxyphenyl)-3-phenylbutanoate (2.01 g, 6.74 mmole) and ethanethiol (2.5 mL, 33.7 mmole) in anhydrous  $CH_2Cl_2$  (67 mL) at 0°C under argon. The yellow solution was warmed to RT and stirred for 3 hr, then was  
 10 recooled to 0°C and quenched with cold 3 N HCl (67 mL). The mixture was stirred for 5 min, then was separated. The aqueous layer was extracted with  $CH_2Cl_2$  (2 x 100 mL), and the combined organic layers were dried ( $Na_2SO_4$ ) and concentrated. Silica gel chromatography (25% EtOAc/hexanes) gave the title compound (1.84 g, 96%) as a colorless oil: TLC  $R_f$  (30% EtOAc/hexanes) 0.47; MS (ES)  $m/e$  285.2 (M  
 15 + H)<sup>+</sup>.

d) Ethyl 3-phenyl-4-[4-(trifluoromethanesulfonyloxy)phenyl]butanoate

Trifluoromethanesulfonic anhydride (1.4 mL, 8.4 mmole) was added rapidly dropwise to a solution of ethyl 4-(4-hydroxyphenyl)-3-phenylbutanoate (1.84 g, 6.47  
 20 mmole) and 2,6-lutidine (1.5 mL, 12.9 mmole) in anhydrous  $CH_2Cl_2$  (32 mL) at -78°C under argon. After 0.5 hr, the yellow solution was warmed to RT and stirred for 1 hr. The reaction was diluted with  $Et_2O$  (150 mL) and washed sequentially with 1.0 N HCl (15 mL), 5%  $NaHCO_3$  (15 mL), and saturated brine (15 mL). Drying ( $MgSO_4$ ), concentration, and silica gel chromatography (15% EtOAc/hexanes) gave  
 25 the title compound (2.62 g, 97%) as a nearly colorless oil: TLC  $R_f$  (20% EtOAc/hexanes) 0.55; MS (ES)  $m/e$  417.0 (M + H)<sup>+</sup>.

e) Ethyl 4-(4-carboxyphenyl)-3-phenylbutanoate

A mixture of ethyl 3-phenyl-4-[4-(trifluoromethanesulfonyloxy)phenyl]butanoate (2.62 g, 6.29 mmole), anhydrous  
 30 KOAc (2.47 g, 25.16 mmole),  $Pd(OAc)_2$  (70.6 mg, 0.31 mmole), dppf (697.4 mg, 1.26 mmole), and anhydrous DMSO (31 mL) was purged with carbon monoxide (three evacuation/ carbon monoxide purge cycles, followed by bubbling carbon monoxide through the mixture for 5 min), then was heated at 70°C under a balloon  
 35 of carbon monoxide. After 3.5 hr, the reaction was diluted with  $H_2O$  (31 mL), cooled in ice, and acidified with 1.0 N HCl (25 mL).  $CH_2Cl_2$  extraction (2 x 100 mL), drying ( $MgSO_4$ ), concentration, and reconcentration from toluene left a

reddish-orange liquid. Silica gel chromatography (1% AcOH in 7:3 toluene/EtOAc) gave the title compound (1.78 g, 91%) as a cream-colored solid: TLC R<sub>f</sub> (1% AcOH in 7:3 toluene/EtOAc) 0.47; MS (ES) m/e 313.2 (M + H)<sup>+</sup>.

- 5 f) Ethyl (±)-4-[4-[[[(1H-benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoate

EDC (230 mg, 1.2 mmole) was added to a solution of ethyl 4-(4-carboxyphenyl)-3-phenylbutanoate (312.4 mg, 1.0 mmole), 2-(methylaminomethyl)benzimidazole dihydrochloride (281 mg, 1.2 mmole), HOBT

- 10 H<sub>2</sub>O (162 mg, 1.2 mmole), and diisopropylethylamine (0.70 mL, 4.0 mmole) in anhydrous CH<sub>3</sub>CN (5 mL) at RT. After 18 hr, the reaction was concentrated, and the brown residue was chromatographed on silica gel (5% MeOH in 1:1 EtOAc/CHCl<sub>3</sub>). The title compound (439.2 mg, 96%) was obtained as a light orange foam: TLC R<sub>f</sub> (5% MeOH in 1:1 EtOAc/CHCl<sub>3</sub>) 0.50; MS (ES) m/e 456.2 (M + H)<sup>+</sup>.

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- g) (±)-4-[4-[[[(1H-Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoic acid

A solution of ethyl (±)-4-[4-[[[(1H-benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoate (439.2 mg, 0.96 mmole) and 1.0 N NaOH (1.2 mL, 1.2 mmole) in EtOH (8.4 mL) was stirred at 50°C. After 24 hr, the reaction was concentrated to dryness and the residue was purified by ODS chromatography (35% MeOH/H<sub>2</sub>O). Concentration and lyophilization gave the title compound (412.2 mg, 86%) as a colorless powder: HPLC (PRP-1®, 35% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) K' = 1.4; MS (ES) 428 (M + H)<sup>+</sup>, 450 (M + Na)<sup>+</sup>. Anal. Calcd for C<sub>26</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>Na · 2.75 H<sub>2</sub>O: C, 62.58; H, 5.96; N, 8.42. Found: C, 62.34; H, 5.84; N, 8.44.

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#### Example 4

- 30 Preparation of (±)-4-[4-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoic acid

- a) tert-Butyl 4-bromobenzoate

- 35 Trifluoromethanesulfonic acid (0.18 mL, 2 mmole) was added dropwise to a mixture of 4-bromobenzoic acid (20.10 g, 100 mmole), anhydrous CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and condensed isobutylene (-78°C; 100 mL), and the resulting mixture was allowed to reflux under a dry ice/acetone condenser. After 40 min, more isobutylene (30



mL) was added, and reflux was continued for an additional 20 min. The reaction was poured into Et<sub>2</sub>O (500 mL) and washed sequentially with 1.0 N KOH (2 x 50 mL), H<sub>2</sub>O (50 mL), and satd brine (50 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (5% EtOAc/hexanes) gave the title compound (15.28 g, 59%) as a light yellow oil: TLC R<sub>f</sub> (5% EtOAc/hexanes) 0.59; MS (ES) m/e 259/257 (M + H)<sup>+</sup>.

b) Methyl 3-[4-(tert-butoxycarbonyl)phenyl]propenoate

A solution of tert-butyl 4-bromobenzoate (5.14 g, 20 mmole), methyl acrylate (9.1 mL, 100 mmole), Pd(OAc)<sub>2</sub> (224.5 mg, 1 mmole), tri-*o*-tolylphosphine (608.8 mg, 2 mmole), and diisopropylethylamine (7.0 mL, 40 mmole) in propionitrile (100 mL) was heated at reflux for 3 hr, then was concentrated on the rotavap. The residue was diluted with Et<sub>2</sub>O (200 mL) and washed sequentially with 1.0 N HCl (2 x 50 mL), 5% NaHCO<sub>3</sub> (50 mL), and satd brine (50 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (15% EtOAc/hexanes) gave the title compound (3.34 g, 64%) as a light yellow solid: TLC R<sub>f</sub> (20% EtOAc/hexanes) 0.51; MS (ES) m/e 263.0 (M + H)<sup>+</sup>.

c) Methyl 3-[4-(tert-butoxycarbonyl)phenyl]propanoate

10% Pd/C (2.71 g, 2.55 mmole) was added to a solution of methyl 3-[4-(tert-butoxycarbonyl)phenyl]propenoate (3.34 g, 12.73 mmole) in EtOAc (65 mL) and MeOH (65 mL), and the mixture was shaken on a Parr apparatus at RT under H<sub>2</sub> (50 psi). After 3 hr, the reaction was filtered through celite®, and the filtrate was concentrated to dryness on the rotavap. Reconcentration from hexanes left the title compound (3.27 g, 97%) as a cloudy, grayish oil: TLC R<sub>f</sub> (20% EtOAc/hexanes) 0.63; MS (ES) m/e 265.0 (M + H)<sup>+</sup>.

d) 3-[4-(tert-Butoxycarbonyl)phenyl]propanoic acid

A mixture of methyl 3-[4-(tert-butoxycarbonyl)phenyl]propanoate (3.27 g, 12.37 mmole), 1.0 N LiOH (14.8 mL, 14.8 mmole), THF (31 mL), and H<sub>2</sub>O (16 mL) was stirred at RT for 1.5 hr, then was concentrated on the rotavap to remove the THF. The aqueous solution was washed with Et<sub>2</sub>O (2 x 30 mL), and the Et<sub>2</sub>O layers were discarded. The aqueous layer was acidified with 1.0 N HCl (ca. 17 mL), and the mixture was extracted with CHCl<sub>3</sub> (3 x 50 mL). Drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration gave the title compound (3.04 g, 98%) as a colorless powder: mp 88.5 - 89.5°C; MS (DCI/NH<sub>3</sub>) m/e 268.0 (M + NH<sub>3</sub>)<sup>+</sup>.

e) N,N-Dimethyl 3-[4-(tert-butoxycarbonyl)phenyl]propanamide  
 EDC (2.09 g, 10.88 mmole) was added to a solution of 3-[4-(tert-butoxycarbonyl)phenyl]propanoic acid (2.27 g, 9.07 mmole), dimethylamine hydrochloride (0.88 g, 10.88 mmole), HOBt · H<sub>2</sub>O (1.47 g, 10.88 mmole), and  
 5 diisopropylethylamine (3.2 mL, 18.14 mmole) in anhydrous CH<sub>3</sub>CN (45 mL) at RT. After 19.5 hr, the reaction was concentrated, and the residue was chromatographed on silica gel (EtOAc). The title compound (2.46 g, 98%) was obtained as a colorless oil: TLC R<sub>f</sub> (EtOAc) 0.52; MS (ES) m/e 278.4 (M + H)<sup>+</sup>.

10 f) Ethyl 4-[4-(tert-butoxycarbonyl)phenyl]-3-(dimethylaminocarbonyl)butanoate  
 A solution of lithium bis(trimethylsilyl)amide in THF (1.0 M, 5.8 mL, 5.8 mmole) was added dropwise over 2.5 min to a solution of N,N-dimethyl 3-[4-(tert-butoxycarbonyl)phenyl]propanamide (1.34 g, 4.83 mmole) in dry THF (48 mL) at -78°C under argon. The yellow solution was stirred at -78°C for 0.5 hr, then ethyl  
 15 bromoacetate (2.7 mL, 24.15 mmole) was added over 15 sec down the walls of the flask (to precool). After 0.5 hr, the reaction was poured into satd NH<sub>4</sub>Cl (50 mL), and the mixture was extracted with EtOAc (2 x 100 mL). Drying (MgSO<sub>4</sub>), concentration, and reconcentration from xylenes left a light yellow oil. Silica gel chromatography (1:1 EtOAc/hexanes) gave the title compound (453.5 mg, 26%) as a  
 20 light yellow oil: TLC R<sub>f</sub> (1:1 EtOAc/hexanes) 0.44; MS (ES) m/e 364.2 (M + H)<sup>+</sup>.

g) Ethyl 4-(4-carboxyphenyl)-3-(dimethylaminocarbonyl)butanoate  
 TFA (2.3 mL) was added all at once to a solution ethyl 4-[4-(tert-butoxycarbonyl)phenyl]-3-(dimethylaminocarbonyl)butanoate (168.6 mg, 0.46  
 25 mmole) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2.3 mL) at 0°C. The solution was stirred at RT for 0.5 hr, then was concentrated to dryness on the rotavap. The residue was reconcentrated from toluene to afford the title compound as a light yellow oil: MS (ES) m/e 308.0 (M + H)<sup>+</sup>.

30 h) Ethyl (±)-4-[4-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoate  
 EDC (105.8 mg, 0.55 mmole) was added to a solution of ethyl 4-(4-carboxyphenyl)-3-(dimethylaminocarbonyl)butanoate (0.46 mmole), 2-(methylaminomethyl)benzimidazole dihydrochloride (129.2 mg, 0.55 mmole),  
 35 HOBt · H<sub>2</sub>O (74.6 mg, 0.55 mmole), and diisopropylethylamine (0.32 mL, 1.84 mmole) in anhydrous CH<sub>3</sub>CN (2.3 mL) at RT. After 22 hr, the reaction was concentrated, and the yellow residue was chromatographed on silica gel (10%

MeOH in 1:1 EtOAc/CHCl<sub>3</sub>). The title compound (191.5 mg, 92%) was obtained as a light yellow oil: TLC R<sub>f</sub> (10% MeOH in 1:1 EtOAc/CHCl<sub>3</sub>) 0.44; MS (ES) m/e 451 (M + H)<sup>+</sup>.

- 5 i) (±)-4-[4-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoic acid

A solution of ethyl (±)-4-[4-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoate (191.5 mg, 0.43 mmole) and 1.0 N LiOH (0.52 mL, 0.52 mmole) in THF (2.2 mL) and H<sub>2</sub>O (1.6 mL) was stirred at RT for 17 hr, then was acidified with TFA (0.10 mL, 1.29 mmole). Concentration left an aqueous residue which was purified by ODS chromatography (17% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA; chromatographed again using 15% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA). Concentration and lyophilization gave the title compound (133.4 mg, 47%) as a colorless powder:  
 10 and H<sub>2</sub>O (1.6 mL) was stirred at RT for 17 hr, then was acidified with TFA (0.10 mL, 1.29 mmole). Concentration left an aqueous residue which was purified by ODS chromatography (17% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA; chromatographed again using 15% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA). Concentration and lyophilization gave the title compound (133.4 mg, 47%) as a colorless powder:  
 15 HPLC (PRP-1®, 20% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) K' = 1.3; MS (ES) m/e 423.2 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub> · 2 CF<sub>3</sub>CO<sub>2</sub>H · 0.5 H<sub>2</sub>O: C, 49.17; H, 4.43; N, 8.49. Found: C, 49.13; H, 4.62; N, 8.52.

#### Example 5

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Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester

- 25 a) (S)-2,3,4,5-Tetrahydro-7-[[[1-(tert-butoxycarbonyl)benzimidazol-2-yl]methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

To a mixture of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid (444 mg, 1.0 mmol), triethylamine (0.1464 mL, 1.05 mmol) in DMF (8 mL), was added dropwise di-tert-butyl dicarbonate (230 mg, 1.05 mmol) in DMF (2 mL). The reaction mixture was stirred at RT for 18 h. An aliquot was assayed to indicate only 50% conversion. Another quantity of triethylamine and di-tert-butyl dicarbonate were added and stirring was continued for another 18 h. An aliquot still indicated some unreacted material, so a third quantity of reagents was added and the reaction was stirred for another 18 h. The reaction mixture was concentrated to dryness and the residual oil was triturated with water, filtered and vacuum dried at

40-50°C, to give a white solid of the title compound (0.442 g, 85%). MS (ES) m/e 522.4 [M+H]<sup>+</sup>.

b) (S)-2,3,4,5-Tetrahydro-7-[[[1-(tert-butoxycarbonyl)benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester

To a solution of the compound of Example 5a, (0.209 g, 0.4 mmol) in dry acetone (10 mL) was added anhydrous potassium carbonate (0.25 g, 1.8 mmol). The reaction mixture was stirred at RT and under argon for 1 h. 2-methoxy-2-methylpropanoic acid chloromethyl ester, US Patent 4,602,012, July 22, 1986, (0.334 g, 2.0 mmol) was then added, followed by tetrabutylammonium iodide (0.03 g, 0.08 mmol). The reaction was stirred at RT under argon for 48 h. It was then filtered and the filtrate was concentrated to a yellow oily residue of the title compound (0.67 g, quantitative yield). TLC R<sub>f</sub> 0.48 (silica gel, 6% methanol in methylene chloride). MS (ES) m/e 652.2 [M+H]<sup>+</sup>.

c) (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester

To a solution of the compound in Example 5b (0.67 g, 1 mmol) in methylene chloride (5 mL) was added TFA (1 mL). The reaction was stirred at RT under argon for 4 h. It was concentrated to dryness, and the residue was evaporated with methylene chloride three times to remove TFA traces, to give the title compound (0.4 g, 73%). This was purified on a flash silica column (step gradient, 2-3% methanol in methylene chloride). The fractions containing the pure compound were collected, concentrated to yield the title compound (65 mg) as an off-white solid. MS (ES) m/e 552.2 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, (CDCl<sub>3</sub>) δ 7.6 (br s, 1H), 7.22 (m, 6H), 6.5 (d, 1H), 5.85 (d, 1H), 5.8 (d, 1H), 5.4 (d, 1H), 5.05 (m, 1H), 4.79 (q, 2H), 4.3 (d, 1H), 3.7 (d, 1H), 3.25 (s, 3H), 3.15 (s, 3H), 3.05 (s, 3H), 3.02 (dd, 1H), 2.7 (dd, 1H), 1.4 (s, 6H). Anal. Calcd for C<sub>28</sub>H<sub>33</sub>N<sub>3</sub>O<sub>7</sub> · 1.25 H<sub>2</sub>O: C, 58.58; H, 6.23; N, 12.20. Found: C, 58.60, H, 5.94, N, 12.00.

#### Example 6

35 Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-(N-hydroxy)acetamide

a) (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazole-2-yl)methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-(N-hydroxy)acetamide

- NaOMe (Aldrich, 25 wt. % solution in MeOH, 2.2 mL, 9.7 mmole) was added to a solution of hydroxylamine hydrochloride (0.67 g, 9.7 mmole) in MeOH (40 mL) at 45°C, and the mixture was stirred for 5 min. Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.82 g, 1.9 mmole) was suspended in MeOH (2 mL) and THF (15 mL) and added dropwise to the above solution. The reaction was then stirred at 45°C for 24 h. The mixture was concentrated in vacuo, and was then treated with 10% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (5 mL). All material dissolved, and then a solid precipitated out. Half of this material was dissolved in the mobile phase by addition of excess TFA and was purified by. preparative HPLC (YMC ODS-AQ, 50 x 250 mm, flow rate = 80 mL/min, 10% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA; t<sub>r</sub> = 57 min) to yield the title compound (91 mg, 22%) as a white solid. MS (ES) m/e 423.1 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 9.06 (bt, J = 4 Hz, 1H), 7.77 (m, 2H), 7.58 (m, 2H), 7.50 (m, 2H), 6.60 (d, J = 10 Hz, 1H), 6.40 (bs, 1H), 5.52 (d, J = 19 Hz, 1H), 5.18 (bt, J = 9 Hz, 1H), 4.85 (d, J = 6 Hz, 1H), 3.83 (d, J = 19 Hz, 1H), 2.95 (s, 3H), 2.60 (dd, J = 17, 9 Hz, 1H), 2.28 (dd, J = 15, 7 Hz, 1H). Anal. Calcd for C<sub>21</sub>H<sub>22</sub>N<sub>6</sub>O<sub>4</sub> · 1.5 C<sub>2</sub>H<sub>5</sub>F<sub>3</sub>O<sub>2</sub> · 1.0 H<sub>2</sub>O: C, 47.14; H, 4.20; N, 13.74. Found: C, 46.95; H, 4.24; N, 13.37.

#### Example 7

##### 25 Preparation of (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 2-(3-Iodophenyl)benzimidazole

- To a cold solution of 3-iodobenzoic acid (5.0 g, 20 mmol) and Et<sub>3</sub>N (3.7 mL, 26 mmol) in THF (50 mL) was added isobutylchloroformate (2.9 mL, 21 mmol). The solution was stirred for 1 h at 10°C. All of the solution was added slowly to a solution of 1,2-diaminobenzene (2.2 g, 20 mmol) in THF (50 mL). After 18 hr, the reaction was concentrated and the residue was partitioned between EtOAc and 5% Na<sub>2</sub>CO<sub>3</sub>. The layers were separated and the EtOAc layer was washed with water. Concentration of the organic layer gave a residue which was treated with EtOAc and allowed to stand for 15 min. Filtration gave a solid which was treated with AcOH (50 mL) and heated to 110°C. After 18 hr, the solution was concentrated. The

residue was treated with EtOAc and the solution was filtered to give the title compound (3.14 g, 50%): MS (ES) m/e 321.2 (M+H)<sup>+</sup>.

b) 2-[(3-Tributylstannyl)phenyl]benzimidazole

- 5        A solution of 2-(3-iodophenyl)benzimidazole (1.0 g, 3.1 mmol),  
bistriethyltin (3.9 mL, 6.2 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (100 mg, 0.14 mmol) in DMF  
(10 mL) was heated to 90°C under argon. After 2 hr, the solution was concentrated.  
The residue was treated with hexane and filtered. EtOAc was added and the solution  
was filtered. The filtrate was concentrated to give the title compound (812 mg,  
10    54%): MS (ES) m/e 485.4 (M+H)<sup>+</sup>.

c) Methyl (±)-2,3,4,5-tetrahydro-1-(tert-butoxycarbonyl)-7-iodo-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

- 15        To a solution of methyl-7-iodo-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-  
acetate (1.6 g, 4.3 mmol) and DMAP (10 mg, 0.08 mmol) in CH<sub>3</sub>CN (10 mL) was  
added di-tert-butyl dicarbonate (2.0 g, 8.6 mmol), and the solution was stirred at RT.  
Additional di-tert-butyl dicarbonate (a total of 8 g, 34.4 mmol) was added  
periodically until the reaction went to completion. Concentration and silica gel  
chromatography gave the title compound (1.8 g, 90%): MS (ES) m/e 497.2 (M+Na)<sup>+</sup>.

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d) Methyl (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-1-(tert-butoxycarbonyl)-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

- 25        A mixture of 2-[(3-tributylstannyl)phenyl]benzimidazole (0.24 g, 0.5 mmol),  
methyl (±)-1-(tert-butoxycarbonyl)-7-iodo-4-methyl-3-oxo-1H-1,4-benzodiazepine-  
2-acetate (0.223 g, 0.7 mmol), CuI (10 mg, 0.05 mmol), and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (40 mg,  
0.05 mmol) in DMF (10 mL) was heated to 100°C under argon. After 18 hr, the  
solution was concentrated. Silica gel chromatography gave the title compound (0.06  
g, 22%): MS (ES) m/e 541.5 (M+H)<sup>+</sup>.

- 30    e) Methyl (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

- 35        A solution of methyl (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-  
1-(tert-butoxycarbonyl)-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.06 g,  
0.11 mmol) in 4 M HCl/dioxane (3 mL) was stirred for 1 hr at RT. The solution was  
concentrated to give the title compound (0.05 g, 100%): MS (ES) m/e 441.4 (M+H)<sup>+</sup>.

f) (±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N NaOH (0.22 mL, 0.22 mmol) was added dropwise to a solution of methyl (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.05 g, 0.11 mmol) in 1:1 MeOH/H<sub>2</sub>O (2 mL) at RT, and the resulting solution was stirred for 18 hr, then was concentrated. The residue was dissolved in H<sub>2</sub>O and the solution was acidified with AcOH to pH 4 (Litmus paper). Filtration gave the title compound (0.005 g, 10%): <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) δ 2.4-2.9 (m, 2H), 3.0-3.1 (s, 3H), 3.8-4.0 (d, 1H), 5.0-5.1 (m, 1H), 5.5-5.6 (d, 1H), 6.7-6.8 (d, 1H), 7.5-8.5 (m, 11H); MS (ES) m/e 427.5 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>25</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub> · 1.5 HCl · 1.0 AcOH · 0.5 H<sub>2</sub>O: C, 58.94; H, 5.22; N, 10.18. Found: C, 59.00; H, 5.15; N, 9.92.

### Example 8

Preparation of (±)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid

a) 2-[[[N-Benzyloxycarbonyl]amino]methyl]phenanthrimidazole

Following the general procedure of Example 7(a), except substituting N-Cbz-glycine for the 3-iodobenzoic acid, and 9,10-diaminophenanthrene for the 1,2-diaminobenzene, the title compound (0.41 g, 45%) was prepared: MS (ES) m/e 382.4 (M+H)<sup>+</sup>.

b) 2-(Aminomethyl)phenanthrimidazole

A solution of 2-[[[N-benzyloxycarbonyl]amino]methyl]phenanthrimidazole (0.2 g, 0.52 mmol) in 30% HBr in acetic acid (0.8 mL) was stirred at RT for 1 hr. The solution was concentrated and the residue was treated with Et<sub>2</sub>O. Filtration gave the title compound (0.138 g, 80%) as an oily residue: MS (ES) m/e 248.3 (M+H)<sup>+</sup>.

c) Methyl (±)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetate

EDC (0.08 g, 0.42 mmol) was added to a solution of 2-(aminomethyl)phenanthrimidazole (0.138 g, 0.42 mmol), methyl (±)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (0.123 g, 0.42 mmol), HOBt · H<sub>2</sub>O (0.063 g, 0.42 mmol) and Et<sub>3</sub>N (0.14 mL, 1 mmol) in anhydrous

DMF (5 mL) at RT. After 18 hr, the reaction was concentrated, and the residue was partitioned between EtOAc and 5% NaHCO<sub>3</sub>. The layers were separated and the organic layer was washed with H<sub>2</sub>O. Drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration gave the title compound (0.2 g, 90%): MS (ES) m/e 522.4 (M+H)<sup>+</sup>.

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d) (±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 7(f), methyl (±)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetate (0.2 g, 0.38 mmol) was saponified and purified to give the title compound (0.014 g, 10%): MS (ES) m/e 508.5 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>29</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub> · 1.0 TFA · 3.0 H<sub>2</sub>O: C, 55.11; H, 4.77; N, 10.37. Found: C, 55.38; H, 5.13; N, 10.74.

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### Example 9

#### Preparation of methyl (±)-7-carboxy-4-(2,2,2-trifluoroethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate

20 a) tert-Butyl 3-[(2,2,2-trifluoroethyl)amino]methyl-4-nitrobenzoate

tert-Butyl 3-bromomethyl-4-nitrobenzoate (2.4 g, 8 mmol) was dissolved in dry THF (50 mL), and 2,2,2-trifluoroethylamine (3 mL, 38 mmol) was added all at once. The orangish-yellow solution was stirred at RT for 40 min, then was concentrated to remove the THF. The residue was diluted with Et<sub>2</sub>O (100 mL) and washed twice with 10 % aqueous Na<sub>2</sub>CO<sub>3</sub> (50 mL) and brine (50 mL). The organic layer was dried (MgSO<sub>4</sub>). Concentration and silica gel chromatography (2.5% - 10% EtOAc/hexanes) gave the title compound (1.6 g, 63%) as a yellow oil: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.21 (d, J = 1.3 Hz, 1H), 8.03 (dd, J = 8.4, 1.3 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 4.20 (s, 2H), 3.24 (q, J = 9.3 Hz, 2H), 1.62 (s, 9H).

30

b) tert-Butyl 3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methyl-4-nitrobenzoate

Di-tert-butyl dicarbonate (2.15 g, 10 mmol) was added all at once to a solution of tert-butyl 3-[(2,2,2-trifluoroethyl)amino]methyl-4-nitrobenzoate (1.6 g, 5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at RT. The reaction was concentrated and heated to 50°C under vacuum for 18 hours. Silica gel chromatography (2% - 5% EtOAc/hexanes) gave the title compound (2 g, 96%) as a yellow oil: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ



7.85-8.15 (m, 3H), 4.75-5.05 (m, 2H), 3.80-4.10 (m, 2H), 1.60 (s, 9H),  
1.15-1.80 (m, 9H).

c) tert-Butyl 4-amino-3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate

10% Pd/C (.4 g, .4 mmol) was added to a solution of tert-butyl 3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methyl-4-nitrobenzoate (2.0 g, 5 mmol) in EtOAc (20 mL), and the mixture was shaken on a Parr apparatus at RT under H<sub>2</sub> (55 psi). After 4 h, the reaction was filtered through celite®, and the filtrate was concentrated to afford the title compound (1.9 g, 99%) as a colorless oil: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.76 (dd, J = 8.5 Hz, 1.8 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 4.53 (s, 2H), 3.69 (m, 2H), 1.58 (s, 9H), 1.51 (m, 9H).

d) tert-Butyl (±)-4-[2-(1,4-dimethoxy-1,4-dioxobutyl)amino]-3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate

A solution of tert-butyl 4-amino-3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate (1.9 g, 5 mmol) and dimethylacetylene dicarboxylate (0.58 mL, 5.5 mmol) in MeOH (10 mL) was heated at reflux for 60 min, then was cooled to RT. The resulting solution was combined with MeOH (20 mL) and 10% Pd/C (0.5 g, .5 mmol), and the mixture was shaken on a Parr apparatus at RT under H<sub>2</sub> (50 psi). After 3 h, the reaction was filtered through celite®, and the filtrate was concentrated on the rotavap. The title compound (1.6 g, 62%) was obtained as a faintly yellow oil: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.85 (dd, J = 8.4, 2.0 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.15 (br s, 1H), 4.55-4.70 (m, 2H), 4.40 (1/2 AB, J = 15.3 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.35-3.50 (m, 2H), 2.95 (dd, J = 16.9, 6.8 Hz, 1H), 2.84 (dd, J = 16.9, 6.9 Hz, 1H), 1.56 (s, 18H).

e) Methyl (±)-7-carboxy-4-(2,2,2-trifluoroethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate

TFA (7 mL) was added all at once to a solution of tert-butyl (±)-4-[2-(1,4-dimethoxy-1,4-dioxobutyl)amino]-3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate (1.6 g, 3 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0°C, and the faintly yellow solution was warmed to RT. After 2 h, the solution was concentrated on the rotavap, and the residue was reconcentrated from toluene (to remove residual TFA). The resulting oil was combined with toluene (10 mL) and Et<sub>3</sub>N (2 mL, 15 mmol), and the mixture was heated to reflux under argon. After 18 hr the solution was allowed to cool and was concentrated to dryness under

vacuum. The residue was dissolved in a minimum of MeOH (ca. 15 mL) at reflux, diluted with H<sub>2</sub>O (10 mL), and acidified with glacial AcOH (4 drops). The mixture was kept in the refrigerator overnight then was filtered. The solid was dried under high vacuum to afford the title compound (0.80 g, 76%) as a tan powder: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.61 (2, 1H), 7.57 (dd, J = 8.5, 2 Hz, 1H), 6.63 (d, J = 2 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 5.59 (d, J = 16.7 Hz, 1H), 5.25 (m, 1H), 4.28 (m, 2H), 4.15 (d, J = 16.7 Hz, 1H), 3.61 (s, 3H), 2.86 (dd, J = 16.8, 8.7 Hz, 1H), 2.74 (dd, J = 16.8, 5.4 Hz, 1H).

10 f) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate

EDC (0.16 g, 0.86 mmol) was added at RT to a solution of methyl (±)-7-carboxy-4-(2,2,2-trifluoroethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (0.20 g, 0.71 mmol), HOBt · H<sub>2</sub>O (0.12 g, 0.86 mmol), 2-aminomethylbenzimidazole dihydrochloride (0.19 g, 0.86 mmol), DIEA (0.5 mL, 2.8 mmol), and acetonitrile (5 mL) under argon. The resulting solution was stirred at RT overnight, then was concentrated. The residue was partitioned between ethyl acetate and water, and the layers were separated. The organic phase was washed with brine, dried (MgSO<sub>4</sub>), and concentrated. Silica gel chromatography (1% - 10% CH<sub>3</sub>OH in CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.12 g, 44%) as a tan solid: NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.59 (t, J = 5 Hz, 1H), 7.61 (m, 2H), 7.50 (m, 2H), 7.16 (m, 2H), 6.57 (d, J = 11.1 Hz, 1H), 6.17 (d, J = 5 Hz, 1H), 5.53 (d, J = 16.7 Hz, 1H), 5.13 (m, 1H), 4.75 (m, 2H), 4.10 (m, 2H), 3.62 (s, 3H), 2.94 (dd, J = 16.8, 8.5 Hz, 1H), 2.69 (dd, J = 16.8, 5.4 Hz, 1H).

25 g) (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

A solution of methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate (0.12 g, 0.25 mmol) and lithium hydroxide monohydrate (0.017 g, 0.4 mmol) in THF (10 mL), CH<sub>3</sub>OH (2 mL), and H<sub>2</sub>O (2 mL) was stirred at RT overnight. It was then concentrated and the residue was dissolved in water. The solution was brought to pH 4 with 3 N HCl, then was refrigerated for 1 hour. The resulting solid was collected by filtration and dried to give the title compound (0.11 g, 90%) as a white solid: Ms (ES) m/e 476 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>F<sub>3</sub>O<sub>4</sub> · 1.25 H<sub>2</sub>O: C, 53.07; H, 4.55; N, 14.06. Found: C, 52.85; H, 4.36; N, 13.98.

Example 10

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate

10        Using the procedures of Example 9(f), except substituting 2-(methylaminomethyl)benzimidazole dihydrochloride for the 2-aminomethylbenzimidazole dihydrochloride, the title compound was prepared: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.67 (m, 2 H), 7.37 (m, 2 H), 7.25 (m, 2 H), 6.54 (d, J = 8 Hz, 1 H), 5.46 (d, J = 16.7 Hz, 1 H), 5.20 (m, 1 H), 5.04 (s, 2 H), 4.71 (m, 1 H),  
15    4.17 (m, 1 H), 3.94 (m, 1 H), 3.92 (d, J = 16.7, 1 H), 3.74 (s, 3 H), 3.23 (s, 3 H), 2.98 (m, 1 H), 2.74 (m, 1 H).

b) (±)-2,3,4,5-Tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

20        Using the procedure of Example 9(g), methyl (±)-2,3,4,5-tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound: MS (ES) m/e 490.2 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>22</sub>N<sub>3</sub>F<sub>3</sub>O<sub>4</sub> · 2.25 H<sub>2</sub>O: C, 52.12; H, 5.04; N, 13.21. Found: C, 52.00; H, 5.12; N, 13.09.

25

Example 11

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

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a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate

35        Using the procedures of Example 9(f), except substituting 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride for the 2-aminomethylbenzimidazole dihydrochloride, the title compound was prepared: MS (ES) m/e 505.2 (M + H)<sup>+</sup>.

b) (±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

- 5 Using the procedure of Example 9(g), methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound: MS (ES) m/e 491.2 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>F<sub>3</sub>O<sub>4</sub> · 2 7/8 H<sub>2</sub>O: C, 48.73; H, 4.97; N, 15.50. Found: C, 48.50; H, 4.59; N, 15.33.

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### Example 12

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylanino]carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylanino]carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

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EDC (0.10 g, 0.55 mmol) was added at RT to a solution of methyl 7-carboxy-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.14 g, 0.3 mmol), 2-(methylaminomethyl)benzimidazole dihydrochloride (0.12 g, 0.51 mmole), HOBt · H<sub>2</sub>O (0.072 g, 0.55 mmol), and DIEA (0.32 mL, 1.84 mmole), in DMF (5 mL) under argon. The resulting solution was stirred at RT overnight, then was concentrated. The residue was partitioned between ethyl acetate and water, and the layers were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. Silica gel chromatography gave the title compound (0.11 g, 59%) as a colorless foam: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.62 (m, 2H), 7.31 (m, 2H), 7.20 (d, J = 8.1 Hz, 1H), 7.07 (s, 1H), 6.65 (d, J = 7.9 Hz, 1H), 6.60 (s, 1H), 6.55 (d, J = 7.9 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 5.90 (d, J = 5.4 Hz, 2H), 5.26 (d, J = 16.5 Hz, 1H), 5.02 (m, 1H), 4.93 (d, J = 14.6, 1H), 4.83 (d, J = 14.6 Hz, 1H), 4.51 (d, J = 5 Hz, 1H), 3.74 (s, 3H), 3.71 (m, 1H), 3.60 (m, 1H), 3.58 (d, J = 16.5 Hz, 1H), 3.18 (s, 3H), 2.99 (dd, J = 16, 6.8 Hz, 1H), 2.70 (m, 1H).

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b) (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylanino]carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

To a solution stirred at RT of methyl (±)-2,3,4,5-tetrahydro-7-  
 [2-((benzimidazol-2-yl)methyl)methylamino]carbonyl]-4-[2-(3,4-  
 methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.11 g, 0.19  
 mmol) in THF (1 mL) was added a solution of lithium hydroxide monohydrate (0.01  
 5 g, 0.23 mmol) in H<sub>2</sub>O (1 mL). The resulting solution was stirred at RT overnight,  
 then was concentrated to dryness. The residue was dissolved in H<sub>2</sub>O and the  
 solution was washed with ethyl acetate, then was brought to pH 4 with 3 N HCl.  
 The resulting precipitate was collected by filtration and dried to give the title  
 compound (0.055 g, 51%) as a white solid. MS (ES) m/e 556.2 [M+H]<sup>+</sup>. Anal.  
 10 Calcd for C<sub>30</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub> · H<sub>2</sub>O: C, 62.82; H, 5.45; N, 12.21. Found: C, 62.69; H, 5.26;  
 N, 12.15.

### Example 13

#### 15 Preparation of (±)-2,3,4,5-tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-  
 (2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate  
 20 EDC (0.27 g, 1.4 mmole) was added at RT to a solution of (±)-2,3,4,5-  
 tetrahydro-7-amino-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.40  
 g, 1.1 mmol), benzimidazole-2-acetic acid (*Archiv. Der Pharmazie* **1960**, 293, 758;  
 0.25 g, 1.4 mmol), HOBt · H<sub>2</sub>O (0.20 g, 1.5 mmol), and DIEA (0.35 mL, 2 mmol) in  
 acetonitrile (10 mL). The resulting solution was stirred for 2 days, then was  
 25 concentrated to dryness. The residue was partitioned between ethyl acetate and  
 water, and the layers were separated. The organic phase was washed with brine,  
 dried (MgSO<sub>4</sub>), and concentrated. Silica gel chromatography (1% - 10% CH<sub>3</sub>OH in  
 CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.21 g, 36%) as an amber foam: MS (ES) m/e  
 512.2 [M+H]<sup>+</sup>.

30 b) (±)-2,3,4,5-Tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-  
 phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

A solution of methyl (±)-2,3,4,5-tetrahydro-7-[[2-(benzimidazol-2-  
 yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.21 g,  
 35 0.41 mmole) and lithium hydroxide monohydrate (0.022 g, 0.52 mmol) in THF (10  
 mL) and H<sub>2</sub>O (2 mL) was stirred at RT overnight, then was then concentrated. The  
 residue was dissolved in water and the solution was washed with ethyl acetate, then

was brought to pH 4 with 3 N HCl. The resulting precipitate was collected by filtration and dried to give the title compound (0.12 g, 59%) as an off-white solid: MS (ES) m/e 498.2 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> · 1.5 H<sub>2</sub>O: C, 64.11; H, 5.76; N, 13.35. Found: C, 64.36; H, 5.57; N, 13.21.

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#### Example 14

##### Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetamide

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a) (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetamide

Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (330 mg, 0.76 mmole) in dry MeOH (10 mL) was cooled in an ice bath as ammonia was bubbled into the solution for 0.5 hr. The reaction was then allowed to sit stoppered at RT for 18 hr. After concentration, the residue was purified by silica gel flash chromatography (90:10 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to give the title compound (52%) as a white solid: MS (ES) m/e 421.2 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub> · 1.5 H<sub>2</sub>O: C, 59.05; H, 6.08; N, 18.78. Found: C, 58.90; H, 6.04; N, 18.45.

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#### Example 15

##### Preparation of (±)-5-[[2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

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a) Methyl (±)-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

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Methyl (±)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (1.0 g, 2.6 mmole) was suspended in toluene (10 mL), and N,N-dimethylformamide-di-tert-butyl acetal (5 mL, 20.8 mmole) was added dropwise. The reaction mixture was heated at 80°C for 1.5 hr, then was cooled to RT and poured into 5% Na<sub>2</sub>CO<sub>3</sub> solution. The layers were separated, and the aqueous was extracted with toluene (2 x). The combined organic layers were

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washed with brine, dried over  $\text{MgSO}_4$ , filtered and evaporated to give the title compound (0.91 g, 82%). MS (ES)  $m/e$  439.2  $[\text{M}+\text{H}]^+$ .

5 b) ( $\pm$ )-2,3,4,5-Tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

A solution of methyl ( $\pm$ )-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (1.5 g, 3.4 mmole) in ethylene glycol dimethyl ether (160 mL) was treated with  $\text{H}_2\text{O}$  (20 mL) and 0.91 N NaOH (5 mL). The reaction was stirred under argon at RT for 24 hr, then was acidified to pH 10 3 with glacial AcOH, concentrated to a small volume (10 mL), and poured into ice  $\text{H}_2\text{O}$ . The precipitated solid was collected and dried giving the title compound in quantitative yield. MS (ES)  $m/e$  425.2  $[\text{M}+\text{H}]^+$ .

15 c) ( $\pm$ )-2,3,4,5-Tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-[N-(2-cyanoethyl)acetamide]

A solution of ( $\pm$ )-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid (1.2 g, 2.6 mmole) in dry DMF (12 mL) under argon was treated with diisopropylethylamine (0.65 g, 5 mmole), EDC (0.764 g, 4 mmole) and HOBt  $\cdot$   $\text{H}_2\text{O}$  (0.54g, 4 mmole). The resulting solution 20 was stirred for 10 min, then was treated with a solution of 3-aminopropionitrile fumarate in dry DMF (2 mL) containing diisopropylethylamine (0.85 g, 6.6 mmole). The reaction was stirred under argon for 18 hr, then was concentrated to dryness. The residue was partitioned between  $\text{H}_2\text{O}$  and EtOAc, and the layers were separated. The organic layer was washed with brine, dried over  $\text{MgSO}_4$ , filtered and 25 concentrated. The oily residue was purified by silica gel flash chromatography (98:2  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) to give the title compound (750 mg, 50%): MS (ES) 477.2  $[\text{M}+\text{H}]^+$ .

d) ( $\pm$ )-1-(2-Cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

30 A solution of ( $\pm$ )-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-[N-(2-cyanoethyl)acetamide] (750 mg, 1.3 mmole) in dry THF (15 mL) under argon was treated with triphenylphosphine (1.14 g, 4.6 mmole), trimethylsilylazide (0.52 g, 4.6 mmole), and diethylazodicarboxylate (0.8 mL, 4.6 mmole) at RT under argon. After 50 hr, the reaction was concentrated 35 to dryness, and the residue was purified by silica gel flash chromatography (98.5:1.5  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) to give the title compound (0.56g, 86%): MS (ES)  $m/e$  502.2  $[\text{M}+\text{H}]^+$ .

e) (±)-1-(2-Cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

A solution of (±)-1-(2-cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole (0.5 g, 1 mmole) in  $\text{CH}_2\text{Cl}_2$  (20 mL) at RT under argon was treated with 4 M HCl in dioxane (10 mL). After 20 hr, the reaction was concentrated to dryness, and the residue was diluted with 5%  $\text{Na}_2\text{CO}_3$ . The solution was extracted with EtOAc, and the EtOAc layer was discarded. The aqueous layer was acidified with dil HCl and extracted with EtOAc (3x). The combined EtOAc extracts were washed with brine, dried over  $\text{MgSO}_4$ , and evaporated to yield the title compound (0.36g, 81%): MS(ES) m/e 445.4  $[\text{M}+\text{H}]^+$ .

f) (±)-1-(2-Cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

A solution of (±)-1-(2-cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole (360 mg, 0.8 mmole) dry DMF (5 mL) was treated under argon with DIEA (129 mg, 1 mmole), EDC (172 mg, 0.9 mmole) and HOBt ·  $\text{H}_2\text{O}$  (122 mg, 0.9 mmole). The reaction was stirred at RT for 10 min, then a solution of 2-aminomethylbenzimidazole dihydrochloride hydrate (352 mg, 1.6 mmole) in DMF (2 mL) containing DIEA (413 mg, 3.2 mmole) was added. After 20 hr, the reaction was concentrated to dryness and the residue was partitioned between  $\text{H}_2\text{O}$  and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by silica gel flash chromatography (95:5  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) to give the title compound (120 mg, 21%): MS (ES) m/e 575.2  $[\text{M}+\text{H}]^+$ .

g) (±)-5-[[2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

A solution of (±)-1-(2-cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole (100 mg, 0.2 mmole) in MeOH (1 mL) was treated with thiophenol (0.02 mL) followed by 1 N NaOH solution (2.2 mL). After 3 hr, the reaction was concentrated to dryness, and the residue was purified by silica gel preparative TLC (85:15  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ). The isolated product was dissolved in  $\text{H}_2\text{O}$ ,



and the solution was filtered to remove insoluble materials. The filtrate was treated with 2 drops of glacial AcOH. The precipitated solid was collected and dried to give the title compound (45 mg, 41%): MS (ES)  $m/e$  522.2  $[M+H]^+$ . Anal. Calcd for  $C_{30}H_{31}N_5O_4 \cdot 2.25 H_2O$ : C, 56.15; H, 5.52; N, 19.65. Found: C, 56.51; H, 5.05; N, 19.72.

### Example 16

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[4-[(2-carboxybenzoyl)amino]but-1-yl]-1H-1,4-benzodiazepine-2-acetic acid

a) N-[[2-(N-4-hydroxybut-1-yl)aminomethyl-4-tert-butoxycarbonyl]phenyl]-L-aspartic acid  $\beta$ -methyl ester

A mixture of N-[[2-formyl-4-tert-butoxycarbonyl]phenyl]-L-aspartic acid  $\beta$ -methyl ester (WO 95/18619; 2.55 g, 7.26 mmol), 4 Å molecular sieves, and 4-hydroxybutylamine (0.64 g, 7.26 mmol) in MeOH (35 mL) was stirred under argon at RT for 30 min, then sodium cyanoborohydride (0.49 g, 0.79 mmol) and acetic acid (0.3 mL) were added. The reaction mixture was kept at RT overnight and then the solvent was eliminated in vacuo. The residue was dissolved in  $H_2O$  and the solution was acidified to pH 4 with dil HCl. EtOAc extraction, drying ( $MgSO_4$ ), filtration, and concentration gave the title compound (1.75 g, 57%) as a pale yellow solid: TLC  $R_f$  (4:20:20:56 MeOH/EtOAc/hexane/ $Cl_2CH_2$ ) 0.22;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.55 (s, 9H), 1.56 (m, 2H), 1.80 (m, 2H), 3.01 (m, 4H), 3.55 (m, 2H), 3.70 (s, 3H), 4.05 (m, 1H), 4.40 (m, 1H), 4.55 (m, 1H), 6.81 (d,  $J = 8.4$  Hz, 1H), 7.70 (s, 1H), 7.89 (d,  $J = 8.4$  Hz, 1H).

b) Methyl (S)-7-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-3-oxo-4-(4-hydroxybut-1-yl)-1H-1,4-benzodiazepine-2-acetate

To a solution of N-[[2-(N-4-hydroxybut-1-yl)aminomethyl-4-tert-butoxycarbonyl]phenyl]-L-aspartic acid  $\beta$ -methyl ester (1.75 g, 4.1 mmol) and triethylamine (1.15 mL, 8.2 mmol) in dichloromethane (150 mL) under argon at RT was added benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (2.08 g, 14.7 mmol). The reaction mixture was stirred overnight at RT, then was washed sequentially with ice-cold dil HCl, water, 5% sodium bicarbonate, saturated brine, and then dried ( $MgSO_4$ ). Filtration and concentration left a residue which was purified by silica gel flash column

chromatography (5% methanol:ethyl acetate) to give the title compound (0.631 g, 38%): TLC R<sub>f</sub> (4% MeOH/EtOAc) 0.26; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.46-1.61 (m, 4H), 1.57 (s, 9H), 2.64 (d, J = 6.9 Hz, 1H), 2.66 (dd, J = 15.9, 6.3 Hz, 1H), 2.99 (dd, J = 15.6, 6.9 Hz, 1H), 3.56-3.54 (m, 4H), 3.74 (s, 3H), 3.84 (d, J = 16.2 Hz, 1H), 4.54 (m, 1H), 5.10 (m, 1H), 5.41 (d, J = 16.2 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 1.8 Hz, 1H), 7.67 (dd, J = 8.3, 1.8 Hz, 1H); MS (ES) m/e 407.2 [M+H]<sup>+</sup>; [α]<sub>D</sub> = -185.4° (c = 1, CH<sub>3</sub>OH).

c) Methyl (S)-7-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-3-oxo-4-(4-phthalimidobut-1-yl)-1H-1,4-benzodiazepine-2-acetate

To a solution of methyl (S)-7-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-3-oxo-4-(4-hydroxybut-1-yl)-1H-1,4-benzodiazepine-2-acetate (437 mg, 1.07 mmol) and triphenylphosphine (308 mg, 1.17 mmol) in THF (20 mL) at RT under argon was sequentially added phthalimide (173 mg, 1.17 mmol) and diethyl azodicarboxylate (205 mg, 1.17 mmol). The reaction mixture was stirred overnight at RT, the solvent was removed, and the residue was purified by silica gel flash column chromatography (4:20:20:56 methanol/ethyl acetate/hexane/methylene chloride) to give the title compound (0.430 g, 75%): TLC R<sub>f</sub> (4:20:20:56 MeOH/EtOAc/hexane/Cl<sub>2</sub>CH<sub>2</sub>) 0.32; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.55 (s, 9H), 1.55-1.61 (m, 4H), 2.68 (dd, J = 14.0, 5.7 Hz, 2H), 2.98 (dd, J = 14.0, 6.6 Hz, 1H), 3.46-3.64 (m, 4H), 3.71 (s, 3H), 3.85 (d, J = 16.5 Hz, 1H), 4.63 (d, J = 4.4 Hz, 1H), 5.08 (dd, J = 5.7, 6.6 Hz, 1H), 5.37 (d, J = 16.5 Hz, 1H), 6.48 (d, J = 8.3 Hz, 1H), 7.67 (s, 1H), 7.69 (d, J = 8.3, 1.8 Hz, 1H), 7.72-7.76 (m, 2H), 7.81-7.86 (m, 2H).

d) Methyl (S)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(4-phthalimidobutyl)-1H-1,4-benzodiazepine-2-acetate

To a solution of methyl (S)-7-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-3-oxo-4-(4-phthalimidobutyl)-1H-1,4-benzodiazepine-2-acetate (660 mg, 0.89 mmol) in dichloromethane (20 mL) was added 4 N HCl/dioxane (5 mL, 20 mmol) at RT under argon. The reaction mixture was stirred for 18 hr. The suspension was concentrated to give the title compound as an off-white solid (425 mg, 98%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.55-1.61 (m, 4H), 2.71 (dd, J = 14.1, 6.0 Hz, 2H), 3.01 (dd, J = 14.1, 6.3 Hz, 1H), 3.50-3.65 (m, 4H), 3.75 (s, 3H), 3.89 (d, J = 16.5 Hz, 1H), 4.68 (d, J = 4.5 Hz, 1H), 5.12 (dd, J = 6.0, 6.3 Hz, 1H), 5.40 (d, J = 16.6 Hz, 1H), 6.41 (bs, 1H), 6.53 (d, J = 8.4 Hz, 1H), 7.69-7.75 (m, 4H), 7.82-7.85 (m, 2H); MS (ES) m/e 480.2 [M+H]<sup>+</sup>.

e) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(4-phthalimidobut-1-yl)-1H-1,4-benzodiazepine-2-acetate

EDC (240 mg, 1.25 mmol) was added to a stirred solution of methyl (S)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(4-phthalimidobut-1-yl)-1H-1,4-benzodiazepine-2-acetate (0.85 g, 0.88 mmol), 2-(aminomethyl)benzimidazole dihydrochloride (230 mg, 1.04 mmol), HOBt · H<sub>2</sub>O (169 mg, 1.25 mmol), and diisopropylethylamine (0.78 mL, 4.5 mmol) in anhydrous acetonitrile (10 mL) at RT. After 19 h, the reaction was concentrated on the rotavap (high vacuum), and the residue was partitioned between H<sub>2</sub>O (5 mL) and EtOAc (20 mL). The layers were separated and the organic layer was washed with H<sub>2</sub>O (5 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>), gave the title compound (230 mg, 43%) as an off-white solid: TLC R<sub>f</sub> (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) 0.30; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.42-1.56 (m, 5H), 2.63 (dd, J = 6.4, 16.2 Hz, 1H), 2.95 (dd, J = 6.7, 16.2 Hz, 1H), 3.33-3.40 (m, 2H), 3.48-3.55 (m, 2H), 3.57 (d, J = 16.5 Hz, 1H), 3.67 (s, 3H), 4.72-4.80 (m, 3H), 5.03 (dd, J = 6.4, 6.7 Hz, 1H), 5.20 (d, J = 16.5 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 7.18-7.21 (m, 2H), 7.52-7.63 (m, 6H); 7.74-7.76 (m, 2H), 9.08 (br s, 1H).

f) (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[4-[(2-carboxybenzoyl)amino]but-1-yl]-1H-1,4-benzodiazepine-2-acetic acid

LiOH (30 mg, 0.71 mmole) was added at RT to a solution of methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(4-phthalimidobut-1-yl)-1H-1,4-benzodiazepine-2-acetate (223 mg, 0.33 mmol) in MeOH (2 mL) and H<sub>2</sub>O (3 mL). The reaction mixture was stirred at RT for 19 hr. Acidification with dil HCl to pH 4 and concentration produced a solid. Filtration gave the title compound (145 mg, 66%) as a white solid: [α]<sub>D</sub> = -100.4° (c = 1, CH<sub>3</sub>OH); <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.32-1.65 (m, 5H), 2.58 (dd, J = 16.4, 6.7 Hz, 1H), 2.90 (dd, J = 16.4, 7.9 Hz, 1H), 3.06 (m, 1H), 3.69 (m, 1H), 4.00 (d, J = 16.7 Hz, 1H), 4.69 (br s, 2H), 5.11 (dd, J = 7.9, 6.7 Hz, 1H), 5.36 (d, J = 16.7 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 7.29 (m, 2H), 7.37 (m, 4H); 7.51 (m, 2H), 7.664 (s, 1H), 7.74 (d, J = 6.8 Hz, 1H); MS (ES) m/e 613.2 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>32</sub>H<sub>32</sub>N<sub>6</sub>O<sub>7</sub> · 1.5 H<sub>2</sub>O: C, 60.08; H, 5.51; N, 113.14. Found: C, 59.77; H, 5.46; N, 12.98.

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Example 17

Preparation of (±)-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid

- 5 a) Methyl (±)-1-(tert-butoxycarbonyl)-7-(4-hydroxy-1-butyn-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate

3-Butyn-1-ol (65 mg, 0.93 mmol), bis(triphenylphosphine)palladium (II) chloride (5 mg, 0.007 mmol), triphenylphosphine (10 mg, 0.038 mmol), and copper(I) iodide (10 mg, 0.052 mmol) were added under an Ar atmosphere to a solution of methyl (±)-2,3,4,5-tetrahydro-1-(tert-butoxycarbonyl)-7-iodo-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (obtained as in example 7c; 440 mg, 0.94 mmol) in triethylamine (34 mL). The reaction mixture was heated to reflux for 4 hr, then was filtered through celite®, and the filtrate was concentrated. The residue was purified by silica gel flash column chromatography (4:20:20:56 MeOH/EtOAc/hexane/Cl<sub>2</sub>CH<sub>2</sub>) to give the title compound (390 mg, 94%) as a pale yellow liquid: TLC R<sub>f</sub> (5% MeOH: Cl<sub>2</sub>CH<sub>2</sub>) 0.37; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.34 (dd, J = 1.8, 8.1 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 5.15-5.23 (m, 1H), 4.75 (d, J = 14.4 Hz, 1H), 3.68 (d, J = 14.4 Hz, 1H), 3.63-3.67 (m, 2H), 3.59 (s, 3H), 3.04 (s, 3H), 2.88 (dd, J = 5.5, 15.2 Hz, 1H), 2.45 (t, J = 6.4 Hz, 2H), 2.26 (dd, J = 9.5, 15.2 Hz, 1H), 2.04 (br s, 1H), 1.34 (br s, 9H); MS (ES) m/e 417 [M+H]<sup>+</sup>.

- b) Methyl (±)-1-(tert-butoxycarbonyl)-7-(4-hydroxybut-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate
- 10% Pd/C (40 mg) was added to a solution of methyl (±)-1-(tert-butoxycarbonyl)-7-(4-(hydroxy-1-butyn-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate (370 mg, 0.89 mmol) in EtOH (20 mL), and the mixture was shaken on a Parr apparatus at RT under H<sub>2</sub> (50 psi). After 12 h, the reaction was filtered through celite®, and the filtrate was concentrated to afford the title compound (350 mg, 94%) as a pale yellow liquid: TLC R<sub>f</sub> (4:20:20:56 MeOH/EtOAc/hexane/Cl<sub>2</sub>CH<sub>2</sub>) 0.55; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.10-7.19 (m, 3H), 5.59-5.77 (m, 1H), 4.85 (d, J = 15.0 Hz, 1H), 3.68-3.60 (m, 5H), 3.12 (s, 3H), 2.85 (dd, J = 5.4, 15.3 Hz, 1H), 2.65 (t, J = 6.4 Hz, 2H), 2.34 (dd, J = 10.0, 15.3 Hz, 1H), 1.30-1.78 (m, 13H); MS (ES) m/e 421 [M+H]<sup>+</sup>.

- 35 c) Methyl (±)-1-(tert-butoxycarbonyl)-7-(4-carboxybut-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate

To a solution of methyl (±)-1-(tert-butoxycarbonyl)-7-(4-hydroxybut-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate (350 mg, 0.82 mmol) in  $\text{CH}_2\text{Cl}_2$  at 0°C was added 2,2,6,6-tetramethyl-oxopiperidinium chloride (*J. Org. Chem.* **1985**, *50*, 3930-3931; 220 mg, 1.1 mmol).  
5 The mixture was stirred for 2 hr at 0°C under Ar atmosphere. 2-Methyl-2-butene (1 mL) was added, followed by the addition of a freshly prepared solution of  $\text{NaClO}_2$  (0.76 g, 6.7 mmol),  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$  (0.78 g, 5.68 mmol) and  $\text{H}_2\text{O}$  (25 mL). The cooling bath was removed, and the mixture was taken up in EtOAc and washed successively with 0.05 M HCl and brine. Drying ( $\text{MgSO}_4$ ), concentration, and silica  
10 gel chromatography (5% AcOH in 4:20:20:56 MeOH/EtOAc/hexane/ $\text{Cl}_2\text{CH}_2$ ), gave the title compound (350 mg, 98%): TLC  $R_f$  (5% AcOH in 4:20:20:56 MeOH/EtOAc/hexane/ $\text{Cl}_2\text{CH}_2$ ) 0.32;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.13-7.18 (m, 3H), 5.60-5.69 (m, 1H), 4.83 (d,  $J = 14.2$  Hz, 1H), 3.76 (d,  $J = 14.2$  Hz, 1H), 3.66 (s, 3H), 3.12 (s, 3H), 2.93 (dd,  $J = 4.5, 15.3$  Hz, 1H), 2.67 (t,  $J = 7.3$  Hz, 2H), 2.36 (t,  $J = 7.3$  Hz, 2H), 2.30-2.34 (m, 1H), 1.95 (q,  $J = 7.3$  Hz, 2H), 1.34 (s, 9H); MS (ES)  $m/e$  435  $[\text{M}+\text{H}]^+$ .

d) Methyl (±)-1-(tert-butoxycarbonyl)-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate  
20 To a stirred and cooled (-10°C) mixture of methyl (±)-1-(tert-butoxycarbonyl)-7-(4-carboxybut-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate (350 mg, 0.8 mmol) and  $\text{Et}_3\text{N}$  (81 mg, 0.8 mmol) in anhydrous THF (8 mL) was added isobutylchloroformate (97 mg, 0.8 mmol). After 10 min, a solution of 1,2-phenylenediamine (1.43 g, 0.9 mmol) in THF (2 mL) was  
25 added. Stirring was continued at RT overnight, then the solvents were evaporated. The residue was dissolved in EtOAc, and the solution was washed sequentially with aqueous  $\text{NaHCO}_3$  and brine. Drying ( $\text{MgSO}_4$ ) and concentration produced a pale yellow solid. This was dissolved in glacial AcOH (5 mL), and the reaction was heated to 60°C. After 3 hr, the mixture was cooled, concentrated, neutralized with  
30 2.5 N NaOH, and extracted with  $\text{CH}_2\text{Cl}_2$ . Drying ( $\text{MgSO}_4$ ), concentration, and silica gel chromatography (gradient 1-5% MeOH/ $\text{CH}_2\text{Cl}_2$ ) gave the title compound (200 mg, 50%): TLC  $R_f$  (4:20:20:56 MeOH/EtOAc/hexane/ $\text{Cl}_2\text{CH}_2$ ) 0.18;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57-7.61 (m, 2H), 7.15-7.28 (m, 4H), 7.08 (s, 1H), 5.60-5.55 (m, 1H), 4.75-4.88 (m, 1H), 3.71 (d,  $J = 14.2$  Hz, 1H), 3.70 (s, 3H), 3.10 (s, 3H),  
35 2.94 (dd,  $J = 4.2, 15.3$  Hz, 1H), 2.85-2.90 (m, 2H), 2.73-2.79 (m, 2H), 2.32-2.36 (m, 1H), 2.15-2.23 (m, 1H), 1.34 and 1.55 (br s, rotamers, 9H); MS (ES)  $m/e$  507  $[\text{M}+\text{H}]^+$ .

e) (±)-7-[3-(Benzimidazol-2-yl)propyl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid

LiOH (17 mg, 0.71 mmole) was added at RT to a solution of methyl (±)-1-(tert-butoxycarbonyl)-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate (200 mg, 0.395 mmol) in MeOH (2 mL) and H<sub>2</sub>O (3 mL). The reaction mixture was stirred at RT for 4 hr. Acidification with dil HCl to pH 4 and concentration produced a white solid. This was dissolved in a mixture of methylene chloride (10 mL) and trifluoroacetic acid (5 mL) at 0°C, and the reaction was kept at 0°C for 30 min. The solvents were evaporated and the residue was triturated with ether and purified by ODS flash chromatography (gradient 10 to 18% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA). Concentration and lyophilization gave the title compound (75 mg, 48%) as a colorless powder: <sup>1</sup>H NMR ((400 MHz, CDCl<sub>3</sub>) δ 7.58-7.61 (m, 2H), 7.37-7.39 (m, 2H), 6.79 (d, J = 8.2 Hz, 1H), 6.68 (s, 1H), 6.39 (d, J = 8.2 Hz, 1H), 5.18 (d, J = 16.8 Hz, 1H), 4.77 (dd, J = 7.0, 7.5 Hz, 1H), 3.63 (d, J = 16.8 Hz, 1H), 3.03-3.19 (m, 3H), 2.97 (s, 3H), 2.83 (dd, J = 7.0, 16.4 Hz, 1H), 2.52-2.56 (m, 2H), 2.08-2.12 (m, 2H); MS (ES) m/e 393.0 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub> · C<sub>2</sub>H<sub>5</sub>FO<sub>2</sub> · 0.5 H<sub>2</sub>O: C, 55.92; H, 5.08; N, 10.89. Found: C, 56.16; H, 4.92; N, 10.88.

#### Example 18

Preparation of (S)-2,3,4,5-tetrahydro-7-[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 4-[(Benzimidazol-2-yl)methyl]aminobutyronitrile

To a stirred mixture of 2-aminomethylbenzimidazole dihydrochloride (0.5 g, 2.2717 mmol) and NaHCO<sub>3</sub> (0.67 g, 7.951 mmol) in dry DMF (10 mL) was added 4-bromobutyronitrile (0.37 g, 2.4989 mmol). After stirring at RT for 24 hr, the mixture was concentrated. The residue was taken up in H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were dried over MgSO<sub>4</sub>, concentrated, and purified by silica gel flash column chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (0.15 g, 35%) as a brown oil: <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) δ 1.82 (m, 2H), 2.45 (t, J = 4 Hz, 2H), 2.85 (t, J = 4 Hz, 2H), 4.11 (s, 2H), 7.14 (m, 2H), 7.50 (m, 2H).

b) Methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-cyanopropyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

To a stirred mixture of 4-[(benzimidazol-2-yl)methyl]aminobutyronitrile (0.159 g, 0.7422 mmol), methyl 2,3,4,5-tetrahydro-7-carboxy-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.217 g, 0.7422 mmol), HOBt · H<sub>2</sub>O (0.120 g, 0.8906 mmol), and i-Pr<sub>3</sub>NEt (0.192 g, 1.4844 mmol) in dry CH<sub>3</sub>CN (7 mL) was added EDC (0.265 g, 0.8906 mmol). After stirring at RT for 48 hr, the mixture was concentrated. The residue was taken up in H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed sequentially with saturated NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, and concentrated to give a brown oil. Silica gel flash column chromatography (3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.261 g, 74%) as an off white foam: <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>): δ 1.95 (m, 2H), 2.66 (dd, J = 16.4, 3.5 Hz, 1H), 2.78 (dd, J = 16.4, 3.5 Hz, 1H), 2.85 (t, J = 8.7 Hz, 2H), 3.45 (t, J = 8.7 Hz, 2H), 3.60 (s, 3H), 3.80 (d, J = 16 Hz, 1H), 4.52 (s, 2H), 4.84 (d, J = 2.9 Hz, 2H), 5.15 (m, 1H), 5.48 (d, J = 16 Hz, 1H), 6.40 (d, J = 3.5 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 7.25 (m, 4H), 7.50 (m, 1H), 7.62 (m, 1H).

c) (S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-cyanopropyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

To a stirred solution of methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-cyanopropyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.261 g, 0.5478 mmol) in MeOH (5 mL) was added 2.5 N NaOH (0.7 mL, 1.6433 mmol). After stirring at RT overnight, the mixture was concentrated. The residue was taken up in H<sub>2</sub>O, and the solution was acidified with 6 N HCl to pH = 4. The white solid was filtered and dried to afford the title compound (0.21 g, 81%): <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>): δ 1.95 (m, 2H), 2.66 (dd, J = 16.4, 3.5 Hz, 1H), 2.78 (dd, J = 16.4, 3.5 Hz, 1H), 2.85 (t, J = 8.7 Hz, 2H), 3.45 (t, J = 8.7 Hz, 2H), 3.80 (d, J = 16 Hz, 1H), 4.52 (s, 2H), 4.84 (d, J = 2.9 Hz, 2H), 5.15 (m, 1H), 5.48 (d, J = 16 Hz, 1H), 6.40 (d, J = 3.5 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 7.25 (m, 4H), 7.50 (m, 1H), 7.62 (m, 1H).

d) (S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

A mixture of (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-cyanopropyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid (0.200 g, 0.4325 mmol) and NH<sub>4</sub>OH (1 mL, 30% solution) in MeOH (5 mL) was hydrogenated over Ra/Ni at RT for 24 hr. The catalyst was filtered off, and the

filtrate was concentrated and purified by reverse phase chromatography (10% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) to give the title compound (0.100 g, 33%) as an off white solid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.45 (m, 2H), 1.72 (m, 2H), 2.54 (dd, J = 16.4, 3.5 Hz, 1H), 2.70 (m, 2H), 2.75 (dd, J = 16.4, 3.5 Hz, 1H), 2.95 (s, 3H), 3.65 (t, J = 8.7 Hz, 2H), 3.85 (d, J = 16 Hz, 1H), 5.05 (s, 2H), 5.15 (m, 1H), 5.48 (d, J = 16 Hz, 1H), 6.65 (d, J = 8.3 Hz, 1H), 7.20 (m, 2H), 7.61 (m, 2H), 7.75 (s, 2H), 7.85 (m, 2H); IR (KBr) 3425, 3000, 3100, 1728, 1675, 1630, 1625, 1613 cm<sup>-1</sup>; MS (ES) m/e 479 (M+H). Anal. Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>6</sub>O<sub>4</sub> · 2 CF<sub>3</sub>CO<sub>2</sub>H: C, 49.30; H, 4.56; N, 11.89. Found: C, 49.22; H, 4.89; N, 11.84.

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Example 19Preparation of (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

15

## a) [(Benzimidazol-2-yl)methyl]aminoacetonitrile

Following the procedure of Example in 18(a), except substituting bromoacetonitrile for the 4-bromobutyronitrile, the title compound was prepared as an off white solid (0.15 g, 35%): <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>): δ 3.71 (s, 2H), 3.98 (s, 2H), 7.14 (m, 2H), 7.50 (m, 2H).

20

## b) Methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 18(b), except substituting [(benzimidazol-2-yl)methyl]aminoacetonitrile for 4-[(benzimidazol-2-yl)methyl]aminobutyronitrile, the title compound was prepared as an off white foam (0.487 g, 66%): <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) δ 2.66 (dd, J = 16.4, 3.5 Hz, 1H), 2.78 (dd, J = 16.4, 3.5 Hz, 1H), 2.92 (s, 2H), 3.60 (s, 3H), 3.80 (d, J = 16 Hz, 1H), 4.52 (s, 2H), 4.84 (d, J = 2.9 Hz, 2H), 5.15 (m, 1H), 5.48 (d, J = 16 Hz, 1H), 6.40 (d, J = 3.5 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 7.25 (m, 4H), 7.50 (m, 2H), 7.62 (m, 2H).

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## c) (S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure in Example 18(c), methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified, and the product was recrystallized from EtOH, to give the title compound as a white solid (0.420 g,

35



89%):  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.66 (dd,  $J$  = 16.4, 3.5 Hz, 1H), 2.78 (dd,  $J$  = 16.4, 3.5 Hz, 1H), 2.92 (s, 2H), 3.80 (d,  $J$  = 16 Hz, 1H), 4.52 (s, 2H), 4.84 (d,  $J$  = 2.9 Hz, 2H), 5.15 (m, 1H), 5.48 (d,  $J$  = 16 Hz, 1H), 6.40 (d,  $J$  = 3.5 Hz, 1H), 6.54 (d,  $J$  = 8.3 Hz, 1H), 7.25 (m, 4H), 7.50 (m, 1H), 7.62 (m, 1H); MS (ES)  $m/e$  465 (M+H) $^+$ . Anal. Calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_6\text{O}_4 \cdot 2 \text{HCl}$ : C, 53.19; H, 4.66; N, 16.18; Found: C, 52.98; H, 4.43; N, 16.53.

#### Example 20

#### 10 Preparation of (S)-2,3,4,5-tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

##### a) Dimethyl (R)-2-trifluoromethanesulfonylsuccinate

To a stirred, cooled (0°C) mixture of dimethyl D-malate (5.5 g, 33.9213 mmol), and dry pyridine (2.82 g, 35.7164 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (55 mL) was added trifluoromethanesulfonic anhydride (10.0 g, 35.7164 mmol) dropwise. After stirring at 0°C for 4 hr, the mixture was quenched with  $\text{H}_2\text{O}$  and the layers were separated. The organic layer was washed sequentially with dil HCl and brine, dried over  $\text{MgSO}_4$ , and concentrated to give title compound (8.50 g, 96%) as a white solid:  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.10 (d,  $J$  = 5.8 Hz, 2H), 3.74 (s, 3H), 3.78 (s, 3H), 5.52 (t,  $J$  = 5.8 Hz, 1H).

##### b) Dimethyl D-(2-cyanophenyl)malate

A mixture of 2-aminobenzonitrile (0.5 g, 4.2323 mmol), 2,6-di-tert-butylpyridine (0.85 g, 4.4439 mmol), and dimethyl (R)-2-trifluoromethanesulfonylsuccinate in 2:1 hexane/chloroform (25 mL) was stirred at RT for 76 hr. The mixture was concentrated, and the residue was taken up in  $\text{H}_2\text{O}$  and extracted with EtOAc. The organic extracts were washed sequentially with 10% HCl and brine, dried over  $\text{MgSO}_4$ , concentrated, and purified by silica gel flash column chromatography (10% EtOAc/hexane) to give the title compound (0.886 g, 80%) as a yellow solid:  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  2.95 (d,  $J$  = 5.8 Hz, 1H), 3.74 (s, 3H), 3.78 (s, 3H), 4.60 (m, 1H), 5.28 (d,  $J$  = 5.8 Hz, 1H), 6.73 (d,  $J$  = 8.5 Hz, 1H), 6.80 (t,  $J$  = 8.5 Hz, 1H), 7.47 (m, 2H).

##### 35 c) Methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate

A solution of dimethyl D-(2-cyanophenyl)malate (10.75 g, 41.0006 mmol) in MeOH (pre-saturated with  $\text{NH}_3$  (g) for 10 min, 100 mL) was hydrogenated over

Ra/Ni at 55 psi for 48 hr. The catalyst was filtered off, and the filtrate was concentrated and purified by silica gel flash column chromatography (40% EtOAc/hexane) to give the title compound (5.03 g, 53%) as an off white solid: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 2.65 (dd, J = 16.3, 7.6 Hz, 1H), 2.99 (dd, 16.3, 5.9 Hz, 1H), 3.74 (s, 3H), 3.95 (dd, J = 16, 6.9 Hz, 1H), 4.79 (m, 1H), 4.95 (dd, J = 16, 5.3 Hz, 1H), 6.55 (t, J = 5.3 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H).

d) Methyl (S)-2,3,4,5-tetrahydro-7-bromo-3-oxo-1H-1,4-benzodiazepine-2-acetate  
 10 A mixture of methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate (5.03 g, 21.4746 mmol) and n-Bu<sub>4</sub>NBr3 (10.35 g, 21.4746 mmol) in CHCl<sub>3</sub> (100 mL) was stirred at RT for 3 hr, then the mixture was concentrated. The residue was taken up in H<sub>2</sub>O, stirred, and filtered to afford the title compound (5.61 g, 83%) as an off white solid: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 2.74 (dd, J = 16.3, 7.6 Hz, 1H),  
 15 3.05 (dd, J = 16.3, 5.9 Hz, 1H), 3.75 (s, 3H), 4.05 (dd, J = 16, 6.9 Hz, 1H), 4.73 (t, J = 5.9 Hz, 1H), 4.86 (dd, J = 16, 5.3 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.75 (t, J = 5.3 Hz, 1H), 7.14 (s, 1H), 7.25 (d, J = 7.6 Hz, 1H).

e) Methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate  
 20 A mixture of methyl (S)-2,3,4,5-tetrahydro-7-bromo-3-oxo-1H-1,4-benzodiazepine-2-acetate (1.5 g, 4.77905 mmol), 2-(methylaminomethyl)benzimidazole dihydrochloride (2.24 g, 9.5809 mmol), triphenylphosphine (1.26 g, 4.7905 mmol), n-Bu<sub>3</sub>N (6.21 g, 33.5333 mmol), and  
 25 (Ph<sub>3</sub>P)<sub>4</sub>Pd (1.10 g, 0.9581 mmol) in N-methyl 2-pyrrolidinone (20 mL) was flushed with argon and carbon monoxide for 10 min. The mixture was then heated at 100-105°C under a carbon monoxide balloon for 8 hr. The mixture was cooled and acidified with 6 N HCl to pH = 2. The solution was extracted with EtOAc, and the EtOAc layer was discarded. The aqueous layer was neutralized with 30% NaOH  
 30 and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were dried over MgSO<sub>4</sub>, concentrated, and purified by silica gel flash column chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (1.62 g, 80%) as an off white solid: <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) δ 2.65 (dd, J = 16.3, 7.6 Hz, 1H), 2.81 (dd, J = 16.3, 5.9 Hz, 1H), 3.05 (s, 3H), 3.60 (s, 3H), 3.75 (dd, J = 16.3, 6.9 Hz, 1H), 4.78 (s, 2H),  
 35 4.95 (m, 1H), 5.05 (dd, J = 16, 5.3 Hz, 1H), 6.20 (d, J = 5.9 Hz, 1H), 6.55 (d, J = 7.6 Hz, 1H), 7.25 (m, 4H), 7.55 (m, 2H), 8.21 (t, J = 5.3 Hz, 1H).

f) (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

- Following the procedure of Example 18(c), methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (0.060 g, 57%) as an off white solid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 2.52 (dd, J = 16.3, 7.6 Hz, 1H), 2.84 (dd, J = 16.3, 5.9 Hz, 1H), 3.20 (s, 3H), 3.75 (dd, J = 16.3, 6.9 Hz, 1H), 4.95 (t, J = 5.9 Hz, 1H), 5.05 (dd, J = 16, 5.3 Hz, 1H), 5.10 (s, 2H), 6.59 (d, J = 7.6 Hz, 1H), 7.12 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.48 (m, 2H), 7.69 (m, 2H), 7.90 (d, J = 5.3 Hz, 1H); IR (KBr) 3600-3100, 3100-2800, 1681, 1613, 1601, 1485, 1445, 1314, 830, 764, 742 cm<sup>-1</sup>; MS (ES) m/e 422 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>: C, 61.91; H, 5.20; N, 17.19. Found: C, 61.57; H, 5.32; N, 17.29.

#### Example 21

15

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[[1-(2-hydroxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

- a) Ethyl 2-[[[(benzimidazol-2-yl)methyl]amino]acetate
- 20 A mixture of 2-aminomethylbenzimidazole dihydrochloride hydrate (4.0 g, 18.1736 mmol), NaHCO<sub>3</sub> (7.63 g, 90.868 mmol), and ethyl 2-bromoacetate (4.55 g, 27.2603 mmol) in dry DMF (60 mL) was stirred at RT for 24 hr, then was concentrated. The residue was taken up in H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were dried over MgSO<sub>4</sub>, concentrated, and purified by silica gel
- 25 flash column chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (0.50 g, 12%) as a brown oil: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 1.95 (s, 3H), 3.48 (s, 2H), 4.50 (m, 4H), 7.25 (m, 2H), 7.35 (m, 1H), 7.73 (m, 1H).

- b) Methyl (S)-2,3,4,5-tetrahydro-7-[[[[1-(2-acetyloxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate
- 30

- Following the procedure of Example 18(b), except substituting ethyl 2-[[[(benzimidazol-2-yl)methyl]amino]acetate for the 4-[(benzimidazol-2-yl)methyl]aminobutyronitrile, the title compound (0.251 g, 78.5%) was prepared as a white solid: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 1.95 (s, 3H), 2.66 (dd, J = 16.4, 3.5 Hz, 1H), 2.95 (s, 3H), 3.05 (dd, J = 16.4, 3.5 Hz, 1H), 3.60 (d, J = 16 Hz, 1H), 3.75 (s, 3H), 4.45 (d, J = 5.9 Hz, 2H), 4.62 (s, 2H), 4.92 (t, J = 5.9 Hz, 2H), 5.10 (m, 1H),
- 35

5.40 (d, J = 16 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 7.32 (m, 3H), 7.60 (m, 2H), 7.71 (m, 1H), 8.15 (t, J = 5.3 Hz, 1H).

c) (S)-2,3,4,5-Tetrahydro-7-[[[1-(2-hydroxyethyl)benzimidazol-2-

5 yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

To a stirred, partial suspension of methyl (S)-2,3,4,5-tetrahydro-7-[[[1-(2-acetyloxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.241 g, 0.475 mmol) in THF (5 mL) was added 1.0 N LiOH (1.4 mL, 1.425 mmol). After stirring at RT overnight, the mixture was  
 10 concentrated. The residue was taken up in H<sub>2</sub>O and acidified with AcOH to pH = 4. The off-white solid was filtered and triturated with acetone to afford the title compound (0.16 g, 75%) as a white solid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 2.54 (dd, J = 16.4, 3.5 Hz, 1H), 2.95 (s, 3H), 3.05 (dd, J = 16.4, 3.5 Hz, 1H), 3.60 (d, J = 16 Hz, 1H), 4.45 (d, J = 5.9 Hz, 2H), 4.62 (s, 2H), 4.92 (t, J = 5.9 Hz, 2H), 5.10 (m,  
 15 1H), 5.40 (d, J = 16 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 7.32 (m, 3H), 7.60 (m, 2H), 7.71 (m, 1H), 8.15 (t, J = 5.3 Hz, 1H); MS (ES) m/e 452 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub> · 0.75 H<sub>2</sub>O: C, 59.71; H, 5.72; N, 15.14. Found: C, 59.65, H, 5.70; N, 14.88.

20

#### Example 22

Preparation of (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-[[4-(2-carboxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

25

a) 4-[[[(Benzimidazol-2-yl)methyl]amino]butyl]phthalimide

A mixture of 2-aminomethylbenzimidazole dihydrochloride hydrate (22.10 g, 100.7269 mmol), NaHCO<sub>3</sub> (42.40 g, 503.6347 mmol), and 4-bromobutylphthalimide (34.10 g, 120.8723 mmol) in dry DMF (250 mL) was heated  
 30 at 100-110°C for 6 hr, then was cooled and concentrated. The residue was taken up in H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were dried over MgSO<sub>4</sub>, concentrated, and purified by silica gel flash column chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (10.8 g, 31%) as a brown foam: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 1.65 (m, 2H), 1.85 (m, 2H), 2.75 (t, J = 8.9 Hz, 2H), 3.78 (t, J =  
 35 8.9 Hz, 2H), 4.17 (s, 2H), 7.20 (m, 2H), 7.60 (m, 2H), 7.72 (m, 2H), 7.88 (m, 2H).

b) Methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-[[4-(phthalimido)butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

To a stirred mixture of 4-[[N-(benzimidazol-2-

- 5 yl)methyl]amino]butylphthalimide (1.75 g, 5.0525 mmol), methyl (±)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (1.61 g, 4.2104 mmol), HOBt · H<sub>2</sub>O (0.69 g, 5.0525 mmol), and i-Pr<sub>3</sub>NEt (1.10 g, 8.4209 mmol) in dry CH<sub>3</sub>CN (30 mL) was added EDC (1.50 g, 5.0525 mmol). After stirring at RT for 24 hr, the mixture was concentrated. The residue was taken up in 10 H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were washed sequentially with saturated NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, concentrated, and purified by silica gel flash column chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (2.85 g, 95%) as a yellow foam: <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) δ 1.60 (m, 2H), 2.65 (m, 2H), 2.85 (dd, J = 16.4, 3.5 Hz, 1H), 3.55 (m, 4H), 3.65 (s, 3H), 4.00 (d, J = 16.0 Hz, 1H), 4.18 (q, J = 8.9 Hz, 2H), 4.75 (s, 2H), 5.15 (m, 1H), 5.45 (d, J = 16.0 Hz, 1H), 6.23 (d, J = 5.3 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 7.20 (m, 7H), 7.55 (m, 4H), 7.90 (m, 4H).

- c) Methyl (±)-tetrahydro-7-[[N-[benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

- A mixture of methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-[[4-(phthalimido)butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.50 g, 0.7015 mmol) and hydrazine (0.07 g, 2.1045 25 mmol) in MeOH (5 mL) was refluxed for 6 hr, then was cooled and concentrated. The residue was taken up in H<sub>2</sub>O, acidified to pH = 2 with 6N HCl, and filtered to remove a white solid. This solid was discarded. The aqueous filtrate was extracted with EtOAc, and the EtOAc layer was discarded. The aqueous layer was basified to pH = 9 with Na<sub>2</sub>CO<sub>3</sub>, and extracted with CHCl<sub>3</sub>. The organic layer was dried over 30 MgSO<sub>4</sub> and concentrated to give the title compound (0.41 g, 89%) as an off white solid: <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) δ 1.47 (m, 2H), 1.75 (m, 2H), 2.65 (m, 5H), 2.85 (dd, J = 16.3, 5.9 Hz, 1H), 3.65 (s, 7H), 4.05 (d, J = 16.0 Hz, 1H), 5.05 (s, 2H), 5.15 (m, 1H), 5.45 (d, J = 16, 1H), 6.65 (d, J = 7.6 Hz, 1H), 7.25 (m, 6H), 7.41 (s, 1H), 7.60 (m, 2H), 7.85 (m, 2H).

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d) (±)-2,3,4,5-Tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(2-carboxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

- To a stirred solution of methyl (±)-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.34 g, 0.47 mmol) in THF was added 1.0 N LiOH (1.2 mL). After stirring at RT overnight, the mixture was concentrated, and the residue was acidified with AcOH to pH = 4. The solid was filtered and triturated with acetone/ether to give the title compound (0.130 g, 39%) as a white solid: <sup>1</sup>H NMR(400 MHz, DMSO-d<sub>6</sub>) δ 1.47 (m, 2H), 1.75 (m, 2H), 2.54 (dd, J = 16.3, 3.5 Hz, 1H), 2.65 (m, 2H), 2.85 (dd, J = 16.3, 5.9 Hz, 1H), 3.20 (m, 2H), 3.75 (m, 4H), 4.05 (d, J = 16.0 Hz, 1H), 5.05 (s, 2H), 5.15 (m, 1H), 5.45 (d, J = 16, 1H), 6.65 (d, J = 7.6 Hz, 1H), 7.25 (m, 6H), 7.41 (s, 1H), 7.60 (m, 2H), 7.85 (m, 2H); IR (KBr) 3400, 3326, 3100-3000, 1721, 1637, 1626, 1616, 1607, 1300, 750, 694 cm<sup>-1</sup>; MS (ES) m/e 717 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>40</sub>H<sub>38</sub>N<sub>6</sub>O<sub>8</sub> · 3 H<sub>2</sub>O: C, 63.56; H, 5.87; N, 11.12. Found: C, 63.56; H, 5.83; N, 11.04.

### Example 23

- 20 Preparation of (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

- a) Methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

- To a mixture of methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(phthalimido)butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.409 g, 0.702 mmol), 4-azidosalicylic acid-N-hydroxysuccinimide ester (0.194 g, 0.702 mmol), and i-Pr<sub>3</sub>NEt (0.272 g, 2.106 mmol) in dry 2:1 CH<sub>3</sub>CN/DMF (10 mL) was added EDC (0.25 g, 0.8424 mmol). After stirring at RT for 24 hr, the mixture was concentrated. The residue was taken up in H<sub>2</sub>O, stirred, and filtered to afford, after drying, the title compound (0.204 g, 39%) as an off white solid: <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) δ 1.40 (m, 2H), 1.75 (m, 2H), 2.65 (m, 3H), 2.75 (dd, J = 16.3, 5.9 Hz, 1H), 3.20 (m, 2H), 3.51 (m, 4H), 3.65 (m, 3H), 3.95 (d, J = 16 Hz, 1H), 4.79 (s, 2H), 5.12 (m, 1H), 5.37 (d, J = 16 Hz, 1H),

6.20 (s, 1H), 6.55 (m, 3H), 7.20 (m, 8H), 7.55 (m, 3H), 7.85 (d, J = 7.6 Hz, 1H), 7.98 (s, 1H), 8.75 (s, 1H).

- b) (±)-2,3,4,5-Tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 22(d), methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (0.100 g, 50%) as a white solid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.40 (m, 2H), 1.75 (m, 2H), 2.65 (m, 3H), 2.75 (dd, J = 16.3, 5.9 Hz, 1H), 3.20 (m, 2H), 3.51 (m, 4H), 3.95 (d, J = 16 Hz, 1H), 4.79 (s, 2H), 5.12 (m, 1H), 5.37 (d, J = 16 Hz, 1H), 6.20 (s, 1H), 6.55 (m, 3H), 7.20 (m, 8H), 7.55 (m, 3H), 7.85 (d, J = 7.6 Hz, 1H), 7.98 (s, 1H), 8.75 (s, 1H); MS (ES) m/e 730 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>39</sub>H<sub>39</sub>N<sub>9</sub>O<sub>6</sub> · 2.5 H<sub>2</sub>O: C, 60.46; H, 5.72; N, 16.27. Found: C, 60.46; H, 5.43; N, 15.90.

#### Example 24

- 20 Preparation of 2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetic acid

- a) Methyl 2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetate

To a mixture of methyl (±)-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.40 g, 0.6865 mmol), (+)-biotin (0.17 g, 0.6865 mmol), HOBt · H<sub>2</sub>O (0.11 g, 0.8239 mmol), and i-Pr<sub>2</sub>NEt (0.18 g, 1.3730 mmol) in 1:2 DMF/CH<sub>3</sub>CN (12 mL) was added EDC (0.25 g, 0.8239 mmol). After stirring at RT for 24 hr, the mixture was concentrated. The residue was taken up in H<sub>2</sub>O and extracted with CHCl<sub>3</sub>. The organic extracts were washed sequentially with saturated NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, concentrated, and purified by silica gel flash column chromatography (10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (0.24 g, 44%) as a yellow foam: <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) δ 1.30 (m, 2H), 1.60 (m, 4H), 2.05 (t, J = 8.9 Hz, 2H), 2.60 (m, 3H), 2.68 (dd, J = 16.3, 5.9 Hz, 1H), 3.10 (m, 4H), 3.45 (m, 2H), 3.60

(m, 2H), 3.65 (s, 3H), 4.01 (d, J = 16 Hz, 1H), 4.12 (t, J = 8.9 Hz, 1H), 4.30 (t, J = 8.9 Hz, 1H), 4.78 (s, 2H), 5.10 (m, 1H), 5.45 (d, J = 16 Hz, 1H), 6.20 (d, J = 5.3 Hz, 1H), 6.40 (d, J = 8.9 Hz, 2H), 6.55 (d, J = 7.6 Hz, 1H), 7.25 (m, 9H), 7.45 (m, 1H), 7.55 (m, 1H), 7.70 (t, J = 8.6 Hz, 1H).

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b) 2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetic acid

To a stirred solution of methyl 2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetate (0.24 g, 0.2967 mmol) in 1:2 THF/MeOH (6 mL) was added 1.0 N LiOH (0.44 mL). After stirring at RT overnight, the mixture was concentrated. The residue was taken up in H<sub>2</sub>O and acidified with AcOH to pH = 4. The off-white solid was filtered, and triturated with hot acetone to give the title compound (0.160 g, 68%) as a white solid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.30 (m, 2H), 1.60 (m, 4H), 2.05 (t, J = 8.9 Hz, 2H), 2.60 (m, 3H), 2.68 (dd, J = 16.3, 5.9 Hz, 1H), 3.10 (m, 4H), 3.45 (m, 2H), 3.60 (m, 2H), 4.01 (d, J = 16 Hz, 1H), 4.12 (t, J = 8.9 Hz, 1H), 4.30 (t, J = 8.9 Hz, 1H), 4.78 (s, 2H), 5.10 (m, 1H), 5.45 (d, J = 16 Hz, 1H), 6.20 (d, J = 5.3 Hz, 1H), 6.40 (d, J = 8.9 Hz, 2H), 6.55 (d, J = 7.6 Hz, 1H), 7.25 (m, 9H), 7.45 (m, 1H), 7.55 (m, 1H), 7.70 (t, J = 8.6 Hz, 1H); MS (ES) m/e 795 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>44</sub>H<sub>38</sub>N<sub>4</sub>O<sub>6</sub>S · 1.75 H<sub>2</sub>O: C, 61.04; H, 6.52; N, 13.56. Found: C, 60.89; H, 6.24; N, 13.31.

25

#### Example 25

Preparation of (±)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) (±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure in Example 24(b), methyl (±)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate was saponified to give the title compound (0.250 g, 80%) as an off white solid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.37 (m, 2H), 1.62 (m, 2H), 2.52 (dd, J = 3.5 Hz, 1H), 2.64 (m, 2H), 2.75 (dd, J =



16.3, 5.9 Hz, 1H), 3.51 (m, 4H), 3.91 (d, J = 16 Hz, 1H), 4.98 (s, 2H), 5.05 (m, 1H), 5.37 (d, J = 16 Hz, 1H), 6.53 (d, J = 7.9 Hz, 2H), 7.17 (m, 7H), 7.52 (m, 1H), 7.62 (s, 1H), 7.78 (m, 1H); IR (KBr): 3386, 3100-3000, 1647, 1613, 1403, 740, 699  $\text{cm}^{-1}$ ; MS (ES) m/e 569 (M+H)<sup>+</sup>. Anal. Calcd for  $\text{C}_{32}\text{H}_{36}\text{N}_6\text{O}_4 \cdot 2.75 \text{H}_2\text{O}$ : C, 62.18; H, 6.77; N, 13.60. Found: C, 62.11; H, 6.68; N, 13.57.

### Example 26

Preparation of (±)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

#### a) 3-Iodo-4-azidosalicylic acid-N-hydroxysuccinimide ester

To a stirred mixture of 4-azidosalicylic acid N-hydroxysuccinimide ester (0.500 g, 1.8103 mmol) and silver trifluoroacetate (0.44 g, 1.9913 mmol) in  $\text{CHCl}_3$  (10 mL) was added iodine (0.510 g, 1.9913 mmol). After stirring at RT overnight, the reaction was filtered to remove a solid precipitate. The filtrate was washed sequentially with  $\text{H}_2\text{O}$ , saturated  $\text{NaHCO}_3$ , and brine, then was dried over  $\text{MgSO}_4$ . Concentration gave the title compound (0.703 g, 97%) as a light purple solid:  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  2.98 (s, 4H), 6.83 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H).

#### b) Methyl (±)-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

Following the procedure in Example 22(b), except substituting 3-iodo-4-azidosalicylic acid-N-hydroxysuccinimide ester for the 4-[[[(benzimidazol-2-yl)methyl]amino]butyl]phthalimide, the title compound (0.312 g, 56%) was prepared as a yellow foam:  $^1\text{H}$  NMR (250 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.42 (m, 2H), 1.60 (m, 2H), 2.52 (dd, J = 16.3, 3.5 Hz, 1H), 2.63 (m, 2H), 2.79 (dd, J = 16.3, 5.9 Hz, 1H), 3.25 (s, 2H), 3.55 (m, 6H), 3.65 (s, 3H), 3.95 (d, J = 16 Hz, 1H), 4.75 (s, 2H), 5.02 (m, 1H), 5.35 (d, J = 16 Hz, 1H), 6.14 (d, J = 5.3 Hz, 1H), 6.52 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 7.25 (m, 10H), 7.51 (s, 2H), 7.90 (d, J = 7.9 Hz, 1H), 9.01 (s, 1H).

c) (±)-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure in Example 22(c), methyl (±)-tetrahydro-7-[[N-  
 5 [[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-  
 hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-  
 benzodiazepine-2-acetate was saponified. Purification by silica gel flash column  
 chromatography (0.5, 0.5, 9.5 AcOH/MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.170  
 g, 58%) as an off white solid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.42 (m, 2H), 1.60  
 10 (m, 2H), 2.52 (dd, J = 16.3, 3.5 Hz, 1H), 2.63 (m, 2H), 2.79 (dd, J = 16.3, 5.9 Hz,  
 1H), 3.25 (s, 2H), 3.55 (m, 6H), 3.95 (d, 16, 1H), 4.75 (s, 2H), 5.02 (m, 1H), 5.35 (d,  
 J = 16 Hz, 1H), 6.14 (d, J = 5.3 Hz, 1H), 6.52 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 7.9  
 Hz, 1H), 7.25 (m, 10H), 7.51 (s, 2H), 7.90 (d, J = 7.9 Hz, 1H), 9.01 (s, 1H); MS (ES)  
 m/e 856 (M+H)<sup>+</sup>; IR (KBr): 3360, 3100-3000, 2116, 1704, 1643, 1610, 1586, 1477,  
 15 1305, 1274, 766, 700 cm<sup>-1</sup>. Anal. Calcd for C<sub>39</sub>H<sub>33</sub>N<sub>9</sub>O<sub>6</sub> · 4.5 H<sub>2</sub>O: C, 50.01; H, 5.06;  
 N, 13.46. Found: C, 50.19; H, 5.01; N, 13.12.

### Example 27

20 Preparation of 5-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-  
 benzimidazole-2-aminoacetic acid

a) Methyl 5-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-  
 benzimidazole-2-aminoacetate

25 Diisopropylethylamine (1.1 mL, 6.48 mmol) was added to a stirred solution  
 of methyl 5-carboxy-benzimidazole-2-aminoacetate (0.24 g, 0.96 mmol), 2-  
 (methylaminomethyl)benzimidazole bis-trifluoroacetate (0.56 g, 1.44 mmol), HOBt ·  
 H<sub>2</sub>O (0.19 g, 1.44 mmol), and EDC (0.28 g, 1.44 mmol) in anhydrous DMF (8 mL)  
 at RT. After 23 h, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and  
 30 washed sequentially with 5% NaHCO<sub>3</sub> (30 mL) and brine (30 mL). Drying  
 (MgSO<sub>4</sub>), concentration, and silica gel chromatography (10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave  
 the title compound (0.16 g, 42%) as an off-white solid: MS (ES) m/e 393.0  
 (M+H)<sup>+</sup>.

35 b) 5-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-  
 aminoacetic acid

1.0 N LiOH (1.0 mL, 1.0 mmol) was added dropwise at RT to a mixture of methyl 5-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-aminoacetate (0.16 g, 0.41 mmol) in THF (10 mL) and H<sub>2</sub>O (10 mL). After 1 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (1.0 mL). The solid was collected, washed with cold H<sub>2</sub>O, and air dried to give the title compound (0.15 g, 100%) as an off white solid: MS (ES) m/e 379.2 (M+H)<sup>+</sup>.

#### Example 28

10

#### Preparation of (±)-2,3,4,5-Tetrahydro 7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

15 a) Methyl (±)-2,3,4,5-tetrahydro 7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

Diisopropylethylamine (0.94 mL, 5.4 mmol) was added to a stirred solution of methyl (±)-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid (0.39 g, 1.08 mmol), 2-(methylaminomethyl)benzimidazole bis(trifluoroacetate) (0.42 g, 1.08 mmol), HOBT · H<sub>2</sub>O (0.22 g, 1.62 mmol), and EDC (0.31 g, 1.62 mmol) in anhydrous DMF (8 mL) at RT. After 23 h, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and washed sequentially with 5% NaHCO<sub>3</sub> (2 x 25 mL) and brine (25 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (7% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.39 g, 71%) as a white solid: MS (ES) m/e 506.4 (M+H)<sup>+</sup>.

b) (±)-2,3,4,5-Tetrahydro 7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

30 1.0 N LiOH (1.0 mL, 1.0 mmol) was added dropwise at RT to a mixture of methyl (±)-2,3,4,5-tetrahydro 7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.38 g, 0.75 mmol) in THF (10 mL) and H<sub>2</sub>O (10 mL). After 50 min, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (2.5 mL). The solid was collected, washed with a cold H<sub>2</sub>O, and air dried to give the title compound (0.27 g, 73%) as a white solid: MS (ES) m/e 492.2 (M+H)<sup>+</sup>.

Example 29

5 Preparation of (±)-2,3,4,5-Tetrahydro 7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro 7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

10 Diisopropylethylamine (0.79 mL, 4.56 mmol) was added to a stirred solution of methyl (±)-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid (0.33 g, 0.91 mmol), 2-(aminomethyl)benzimidazole dihydrochloride hydrate (0.3 g, 1.36 mmol), HOBt · H<sub>2</sub>O (0.18 g, 1.36 mmol), and EDC (0.26 g, 1.36 mmol) in anhydrous DMF (8 mL) at RT. After 20 h, the reaction  
15 mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (70 mL) and washed sequentially with 5% NaHCO<sub>3</sub> (2 x 20 mL) and brine (20 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (7% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.25 g, 56%) as a white solid: MS (ES) m/e 492.4 (M+H)<sup>+</sup>.

20 b) (±)-2,3,4,5-Tetrahydro 7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N LiOH (1.0 mL, 1.0 mmol) was added dropwise at RT to a mixture of methyl (±)-2,3,4,5-tetrahydro 7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.24 g, 0.49 mmol) in  
25 THF (8 mL) and H<sub>2</sub>O (8 mL). After 2.5 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (1.2 mL). The solid was collected, washed with cold H<sub>2</sub>O, and air dried to give the title compound (0.25 g, 109%) as a white solid: MS (ES) m/e 478.2 (M+H)<sup>+</sup>.

30

Example 30

Preparation of (±)-2,3,4,5-Tetrahydro 7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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a) Methyl (±)-2,3,4,5-tetrahydro 7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

Diisopropylethylamine (0.53 mL, 3.0 mmol) was added to a stirred solution of methyl (±)-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid (0.22 g, 0.61 mmol), 2-(methylamino)methyl-4-azabenzimidazole diacetate (0.29 g, 1.0 mmol), HOBt · H<sub>2</sub>O (0.12 g, 0.91 mmol), and EDC (0.17 g, 0.91 mmol) in anhydrous CH<sub>3</sub>CN (12 mL) at RT. After 21 h, the reaction mixture was concentrated, diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and washed sequentially with 5% NaHCO<sub>3</sub> (2 x 20 mL) and brine (20 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (7% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.147 g, 48%) as a white solid: MS (ES) m/e 507.4 (M+H)<sup>+</sup>.

b) (±)-2,3,4,5-Tetrahydro 7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N LiOH (0.69 mL, 0.69 mmol) was added dropwise at RT to a mixture of methyl (±)-2,3,4,5-tetrahydro 7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.14 g, 0.276 mmol) in THF (8 mL) and H<sub>2</sub>O (8 mL). After 2 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.69 mL). The solid was collected, washed with cold H<sub>2</sub>O, and air dried to give the title compound (0.074 g, 54%) as a white solid: MS (ES) m/e 493.2 (M+H)<sup>+</sup>.

25

### Example 31

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

30

a) Methyl (S)-2,3,4,5-tetrahydro-7-[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Diisopropylethylamine (0.27 mL, 1.53 mmol) was added to a stirred solution of methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate trifluoroacetate (0.14 g, 0.34 mmol), 2-[[1-[(benzimidazol-2-yl)methyl]benzimidazole]methyl]amine bis(trifluoroacetate) (0.17 g, 0.34 mmol),

35

HOBt · H<sub>2</sub>O (0.064 g, 0.48 mmol), and EDC (0.091 g, 0.48 mmol) in anhydrous DMF (10 mL) at RT. After 22 h, the reaction mixture was concentrated, diluted with CH<sub>2</sub>Cl<sub>2</sub> (70 mL), and washed sequentially with 5% NaHCO<sub>3</sub> (2x30 mL) and brine (20 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (7% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.080 g, 43%) as a white solid: MS (ES) m/e 552.2 (M+H)<sup>+</sup>.

b) (S)-2,3,4,5-Tetrahydro-7-[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid  
 1.0 N LiOH (0.36 mL, 0.36 mmol) was added dropwise at RT to a mixture of methyl (S)-2,3,4,5-tetrahydro-7-[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.08 g, 0.14 mmol) in THF (5 mL) and H<sub>2</sub>O (4 mL). After 2 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.69 mL). The solution was lyophilized to a crude product (0.086 g) as a white powder. Purification on C-18 Bond Elute (0%-20% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) afforded the title compound as a white powder: MS (ES) m/e 538.2 (M+H)<sup>+</sup>.

20

Example 32Preparation of (S)-2,3,4,5-Tetrahydro-7-[[bis(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (S)-2,3,4,5-tetrahydro-7-[[bis(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate  
 Diisopropylethylamine (0.22 mL, 1.29 mmol) was added to a stirred solution of methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate trifluoroacetate (0.075 g, 0.26 mmol), bis[(benzimidazol-2-yl)methyl]amine tris(trifluoroacetate) (0.16 g, 0.26 mmol), HOBt · H<sub>2</sub>O (0.05 g, 0.36 mmol), and EDC (0.069 g, 0.36 mmol) in anhydrous CH<sub>3</sub>CN (10 mL) at RT. After 17 h, the reaction mixture was concentrated, diluted with CH<sub>2</sub>Cl<sub>2</sub> (80 mL), and washed sequentially with 5% NaHCO<sub>3</sub> (2 x 20 mL) and brine (20 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (7% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.05 g, 36%) as a white solid: MS (ES) m/e 552.2 (M+H)<sup>+</sup>.

- b) (S)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid
- 1.0 N LiOH (0.23 mL, 0.23 mmol) was added dropwise at RT to a mixture of methyl (S)-2,3,4,5-tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.05 g, 0.09 mmol) in THF (6 mL) and H<sub>2</sub>O (4 mL). After 1 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.3 mL). The solid was collected, washed with cold H<sub>2</sub>O, and air dried to give the title compound (0.048 g, 98%) as a white solid: MS (ES) m/e 538.2 (M+H)<sup>+</sup>.

### Example 33

#### Preparation of (±)-2,3,4,5-tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenethyl)-1H-1,4-benzodiazepine-2-acetic acid

- a) Methyl (±)-2,3,4,5-tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenethyl)-1H-1,4-benzodiazepine-2-acetate
- Diisopropylethylamine (0.3 mL, 1.74 mmol) was added to a stirred solution of methyl (±)-7-carboxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (0.11 g, 0.29 mmol), bis[(benzimidazol-2-yl)methyl]amino tris(trifluoroacetate) (0.18 g, 0.29 mmol), HOBt · H<sub>2</sub>O (0.058 g, 0.43 mmol), and EDC (0.083 g, 0.43 mmol) in anhydrous CH<sub>3</sub>CN (12 mL) at RT. After 21 h, the reaction mixture was concentrated, diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and washed sequentially with 5% NaHCO<sub>3</sub> (2 x 20 mL) and brine (20 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (7% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.13 g, 70%) as a white solid: MS (ES) m/e 642.2 (M+H)<sup>+</sup>.
- b) (±)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenethyl)-1H-1,4-benzodiazepine-2-acetic acid
- 1.0 N LiOH (0.6 mL, 0.6 mmol) was added dropwise at RT to a mixture of methyl (±)-2,3,4,5-tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenethyl)-1H-1,4-benzodiazepine-2-acetate (0.13 g, 0.20 mmol) in THF (5 mL) and H<sub>2</sub>O (5 mL). After 18 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.6 mL). The solution was lyophilized to a crude product (0.092 g, 77%) as

a white powder. ODS chromatography (step gradient, 5%-30% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) afforded the title compound as a white powder: MS (ES) m/e 628.2 (M+H)<sup>+</sup>.

5

Example 34Preparation of ethyl (±)-3-[[[2-(benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate

## 10 a) (±)-4-Ethynyl-2-azetidinone

4-Acetoxy-2-azetidinone (9.0 g, 69.7 mmol) was added slowly to a solution of ethynylmagnesiumchloride (31 mL of a 0.5 M THF solution, 0.55 mmol) at 0°C. After 1.5 h, 1.0 N HCl (100 mL) was added, and the mixture was taken up in EtOAc (300 mL) and washed sequentially with 1.0 N HCl (100 mL), saturated NaHCO<sub>3</sub> (100 mL), and brine (100 mL). After drying (MgSO<sub>4</sub>) and concentration, the title compound (4.57 g, 69%) was obtained as a light brownish solid: MS (ES) m/e 96.0 (M+H)<sup>+</sup>.

## 20 b) Ethyl (±)-3-amino-4-pentynoate

A mixture of (±)-4-ethynyl-2-azetidinone (1.3 g, 13.68 mmol), EtOH (54 mL), and concentrated HCl (6 mL) was heated to reflux for 18 h. The reaction was cooled to RT before adjusting the pH to 8.0 using saturated NaHCO<sub>3</sub>. The reaction was extracted with EtOAc (3 x 70 mL), and the combined EtOAc layers were washed with brine (50 mL). Drying (MgSO<sub>4</sub>) and concentration gave the title compound (1.06 g, 55%) as a brownish liquid: MS (ES) m/e 141.9 (M+H)<sup>+</sup>.

## 30 c) Methyl-[[[2-(benzimidazol-2-yl)ethyl]amino]succinate

3-Carbomethoxypropionylchloride (0.6 g, 4.0 mmol) was added at 0°C to a stirred solution of 2-aminoethylbenzimidazole diacetate (1.13 g, 4.0 mmol) and diisopropylethylamine (2.59 g, 20 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (45 mL). After stirring for 1.5 h at RT, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed sequentially with H<sub>2</sub>O (30 mL), 5% NaHCO<sub>3</sub> (30 mL), and brine (30 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (8% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.2 g, 18%) as a yellow solid: MS (ES) m/e 276.4 (M+H)<sup>+</sup>.

35

## d) [[2-(Benzimidazol-2-yl)ethyl]amino]succinic acid



A mixture of methyl-[[2-(benzimidazol-2-yl)ethyl]amino]succinate (0.2 g, 0.73 mmol), 1.0 N NaOH (1.82 mL, 1.82 mmol) and MeOH (10 mL) was stirred at RT for 24 h, then was concentrated to dryness. H<sub>2</sub>O (5 mL) was added, the solution was neutralized with 1.0 N HCl (1.82 mL), and the resulting solution was lyophilized to give the crude title compound (0.23 g) as an off-white powder: MS (ES) m/e 261.9 (M+H)<sup>+</sup>.

e) Ethyl (±)-3-[[[2-(benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate Diisopropylethylamine (0.32 mL, 1.83 mmol) was added to a stirred solution of ethyl (±)-3-amino-4-pentynoate (0.12 g, 0.88 mmol), [[2-(benzimidazol-2-yl)ethyl]amino]succinic acid (0.19 g, 0.73 mmol), HOBt · H<sub>2</sub>O (0.15 g, 1.1 mmol), and EDC (0.21 g, 1.1 mmol) in anhydrous CH<sub>3</sub>CN (15 mL) and DMF (3 mL) at RT. After 23 h, the reaction mixture was concentrated, diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and washed sequentially with 5% NaHCO<sub>3</sub> (2 x 25 mL) and brine (25 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (7% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.07 g, 25%) as a white solid: MS (ES) m/e 385.4 (M+H)<sup>+</sup>.

#### Example 35

##### 20 Preparation of (±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoic acid

a) (±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoic acid 1.0 N LiOH (0.78 mL, 0.78 mmol) was added dropwise at RT to a mixture of ethyl (±)-3-[[[2-(benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate (0.12 g, 0.31 mmol) in THF (5 mL), H<sub>2</sub>O (5 mL) and CH<sub>3</sub>CN (1 mL). After 3 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.78 mL). The solution was lyophilized to a crude product (0.167 g) as a white powder. ODS chromatography (10% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) afforded the title compound as a white powder: MS (ES) m/e 357.1 (M+H)<sup>+</sup>.

#### Example 36

##### 35 Preparation of (±)-3-[[[4-(4-Azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoic acid (SB-237554)

## a) Methyl (4-azabenzimidazol-2-yl)butyrate

Triethylamine (319 mL, 22.9 mmol) was added to a mixture of 2,3-diaminopyridine (2.5 g, 22.9 mmol) and methyl 4-(chloroformyl)butyrate (3.77 g, 22.9 mmol) in dry THF (50 mL) at 0°C. After stirring for 16 h at RT, the reaction  
5 was concentrated to dryness under vacuum. The residue was dissolved in glacial AcOH (25 mL) and was heated at 110°C. After 93 h, the reaction was allowed to cool to RT and was concentrated under vacuum. The dark brown residue was diluted with H<sub>2</sub>O (40 mL) and CH<sub>2</sub>Cl<sub>2</sub> (40 mL), and the mixture was neutralized to pH 7 using 5 N NaOH. The layers were separated and the aqueous layer was further  
10 extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x100 mL). The combined organic layers were washed sequentially with 5% NaHCO<sub>3</sub> (2 x 30 mL) and brine (30 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (7% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.47, 9%): MS (ES) m/e 220.0 (M+H)<sup>+</sup>.

## 15 b) (4-Azabenzimidazol-2-yl)butyric acid

A mixture of methyl (4-azabenzimidazol-2-yl)butyrate (0.47 g, 2.13 mmol), 1.0 N NaOH (6 mL, 6.0 mmol) and MeOH (10 mL) was stirred at RT for 5.5 h, then was concentrated to dryness. The residue was diluted with H<sub>2</sub>O (2 mL) and neutralized with 1.0 N HCl (0.73 mL). The resulting solid was collected and air  
20 dried to give the title compound (0.32 g, 73%) as a yellow powder: MS (ES) m/e 206.0 (M+H)<sup>+</sup>.

## c) Ethyl (±)-3-[[[N-tert-butoxycarbonyl]glycyl]amino]-4-pentanoate

Diisopropylethylamine (0.92 mL, 5.32 mmol) was added to a stirred solution  
25 of ethyl (±)-3-amino-4-pentynoate (0.3 g, 2.13 mmol), Boc-Gly (0.56 g, 3.19 mmol), HOBt · H<sub>2</sub>O (0.43 g, 3.19 mmol), and EDC (0.61 g, 3.19 mmol) in anhydrous CH<sub>3</sub>CN (15 mL) at RT. After 34 h, the reaction mixture was concentrated, diluted with CH<sub>2</sub>Cl<sub>2</sub> (70 mL), and washed sequentially with 5% NaHCO<sub>3</sub> (2x15 mL) and brine (15 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (1:1  
30 EtOAc/Hexane) gave the title compound (0.5 g, 79%) as a colorless oil: MS (ES) m/e 299.2 (M+H)<sup>+</sup>.

## d) Ethyl (±)-3-[(glycyl)amino]-4-pentanoate trifluoroacetate

A solution of TFA (5 mL) and CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at RT was added all at once  
35 to ethyl (±)-3-[[[N-tert-butoxycarbonyl]glycyl]amino]-4-pentanoate (0.5 g, 1.68 mmol). After 30 min, the solution was concentrated on the rotavap, and the residue

was reconcentrated from toluene (to remove residual TFA) to afford the title compound (0.55g, 106%) as a light yellow syrup: MS (ES) m/e 199.2 (M+H)<sup>+</sup>.

- 5 e) Ethyl (±)-3-[[[4-(4-azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoate  
Diisopropylethylamine (0.94 mL, 5.43 mmol) was added to a stirred solution of ethyl (±)-3-[(glycyl)amino]-4-pentanoate trifluoroacetate (0.55 g, 1.76 mmol), (4-azabenzimidazol-2-yl)butyric acid (0.32 g, 1.55 mmol), HOBt · H<sub>2</sub>O (0.31 g, 2.33 mmol), and EDC (0.45 g, 2.33 mmol) in anhydrous CH<sub>3</sub>CN (15 mL) at RT. After 64 h, the reaction mixture was concentrated, diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and washed  
10 sequentially with 5% NaHCO<sub>3</sub> (2 x 25 mL) and brine (25 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (7% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (0.11 g, 18%) as a white solid: MS (ES) m/e 386.4 (M+H)<sup>+</sup>.

- 15 f) (±)-3-[[[4-(4-Azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoic acid  
1.0 N LiOH (0.71 mL, 0.71 mmol) was added dropwise at RT to a mixture of ethyl (±)-3-[[[4-(4-azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoate (0.11 g, 0.285 mmol) in THF (5 mL), H<sub>2</sub>O (5 mL) and CH<sub>3</sub>CN (1 mL). After 2 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.70 mL). The solution was  
20 lyophilized to a crude product (0.1 g, 100%) as a white powder. ODS chromatography (5% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) afforded the title compound as a white powder MS (ES) m/e 358.4 (M+H)<sup>+</sup>.

#### Example 37

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Preparation of (S)-2,3,4,5-tetrahydro-7-[[[4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

- a) Dimethyl D-malate-O-trifluoromethanesulfonate  
30 A solution of dimethyl-D-malate (12.96 g, 80 mmol) and pyridine (6.8 mL, 84 mmol) in CH<sub>2</sub>Cl<sub>2</sub> dry (50 mL) was added dropwise under argon at 0°C to a solution of trifluoromethanesulfonic anhydride (14.2 mL, 84 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (40 mL) in a flame dried flask. The resulting yellowish-orange mixture was stirred at 0°C for 30 min, and then at RT for 4 hr. The reaction was quenched by adding  
35 H<sub>2</sub>O (50 mL), and the layers were separated. The organic layer was washed sequentially with H<sub>2</sub>O (3 x) and brine. Drying (MgSO<sub>4</sub>) and concentration gave the title compound (22.45 g, 95%) as an off white solid: MS(ES) m/e 295 (M + H)<sup>+</sup>.

## b) Dimethyl-N-(2-cyanophenyl)-D-aspartate

A solution of dimethyl D-malate-O-trifluoromethanesulfonate (22.4 g, 76.2 mmol) in  $\text{CHCl}_3$  (40 mL) and hexanes (40 mL) was added to a solution of 2-aminobenzonitrile (9.0 g, 76.2 mmol) and 2,6-di-tert-butylpyridine in  $\text{CHCl}_3$  (50 mL) and hexanes (50 mL) in a flame dried flask at  $0^\circ\text{C}$  under argon. The resulting mixture was stirred at  $0^\circ\text{C}$  for 30 min, then at RT for 3 days. The solvent was removed in vacuo and the residue was taken into EtOAc and washed sequentially with 5% HCl (10 x) and brine. Drying ( $\text{MgSO}_4$ ), concentration and silica gel flash chromatography (12% EtOAc/hexanes) gave the title compound (12.3 g, 62%) as a clear oil: MS(ES) m/e 263.3 (M + H)<sup>+</sup>.

## c) Methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture of dimethyl-N-(2-cyanophenyl)-D-aspartate (12 g, 45.7 mmol),  $\text{Et}_3\text{N}$  (7.64 mL, 54.84 mmol) and Raney-Ni (46 g, wet, prewashed with  $\text{CH}_3\text{OH}$ ) in  $\text{CH}_3\text{OH}$  (200 mL) was stirred at RT under  $\text{H}_2$  (balloon) for 2 days. The catalyst was removed by filtration and washed with  $\text{CH}_3\text{OH}$  (3 x). Concentration and silica gel flash chromatography (0-5%  $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) gave the title compound (7.93 g, 74 %) as a white solid: MS(ES) m/e 235.3 (M + H)<sup>+</sup>.

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## d) Methyl (S)-2,3,4,5-tetrahydro-7-bromo-3-oxo-1H-1,4-benzodiazepine-2-acetate

Tetrabutylammonium tribromide (5.16 g, 10.7 mmol) was added portionwise to a solution of methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate (2.5 g, 10.7 mmol) in  $\text{CHCl}_3$  (50 mL), and the mixture was stirred at RT for 2 days.  $\text{H}_2\text{O}$  (30 mL) was then added, and the organic layer was separated and washed sequentially with  $\text{H}_2\text{O}$  and brine. Drying ( $\text{MgSO}_4$ ), concentration, and silica gel flash chromatography (0-5%  $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) gave the title compound (1.99 g, 60%) as a white solid: MS(ES) m/e 313.0 (M + H)<sup>+</sup>.

## e) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture containing methyl (S)-2,3,4,5-tetrahydro-7-bromo-3-oxo-1H-1,4-benzodiazepine-2-acetate (624 mg, 2 mmol), 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride (695 mg, 2.8 mmol), DIEA (1.8 mL, 10 mmol), and  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  (126 mg, 0.18 mmol) in NMP (22 mL) was heated to  $110^\circ\text{C}$  under a CO balloon for 48 hr. The solvent was removed on the rotavap (high vacuum) and the residue was purified by silica gel flash chromatography (0.5 - 5%

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CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (170 mg, 19.5%) as a pale yellow solid: MS (ES) m/e 437.5 (M + H)<sup>+</sup>.

- f) (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid
- 5 1.0 M LiOH (0.6 mL, 0.6 mmol) was added dropwise to a solution of methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate (170 mg, 0.39 mmol) in CH<sub>3</sub>OH (5 mL) and THF (5 mL) at RT. The resulting mixture was
- 10 stirred for 20 hr and then was concentrated. The residue was dissolved in H<sub>2</sub>O, acidified with 30% TFA, and purified by ODS chromatography (5% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA). Concentration and lyophilization gave the title compound as an off white powder: [α]<sub>D</sub><sup>25</sup> -74.5° (c = 1, CH<sub>3</sub>OH); MS (ES) m/e 423.2 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>21</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub> · 2 TFA · 1.75 H<sub>2</sub>O: C, 44.03; H, 4.06; N, 12.32. Found:
- 15 C, 44.33; H, 4.04; N, 12.28.

### Example 38

- Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid
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- a) Methyl (S)-2,3,4,5-tetrahydro-7-iodo-3-oxo-1H-1,4-benzodiazepine-2-acetate
- Pyridine-ICl complex: Iodine monochloride (100 mL, 1 M solution in CH<sub>2</sub>Cl<sub>2</sub>) was added slowly to a solution of pyridine (8.5 mL, 105 mmol) in dry
- 25 CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 5°C under argon so that the temperature was maintained between 10 - 15°C. The mixture was stirred at 5 - 10°C for 20 min, then hexanes (50 mL) was added, and the mixture was stirred in the cold bath for another 30 min. The solid was collected by suction filtration, washed sequentially with hexanes and petroleum ether, and dried to afford the reagent (22.5 g) as a yellow, crystalline
- 30 solid.

- Pyridine-ICl complex (1.27 g, 5.28 mmol) was added portionwise to a solution of methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate (1.18 g, 4.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and CH<sub>3</sub>OH (20 mL). The resulting mixture was stirred at RT for 40 min, then 1 M NaHSO<sub>3</sub> (20 mL) was added. The solid was
- 35 collected by suction filtration and washed with Et<sub>2</sub>O. Drying yielded the title compound (1.72 g, quantitative) as an off-white solid: MS (ES) m/e 361.2 (M + H)<sup>+</sup>.

b) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture of methyl (S)-2,3,4,5-tetrahydro-7-iodo-3-oxo-1H-1,4-benzodiazepine-2-acetate (1.08 g, 3 mmol), 2-aminomethylbenzimidazole dihydrochloride hydrate (924 mg, 4.2 mmol), DIEA (2.6 mL, 15 mmol), and (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (211 mg, 0.3 mmol) in NMP (30 mL) was heated to 110°C under a CO balloon for 3 hr. The solvent was removed on the rotavap (high vacuum) and the residue was purified by silica gel flash chromatography (0-7% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound (530 mg, 44%) as an off white solid: MS(ES) m/e 408.1 (M + H)<sup>+</sup>.

c) (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 37(f), except substituting methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate for methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate, the title compound (66%) was prepared as a white powder:  $[\alpha]_D^{25}$  -145.3° (c = 1, CH<sub>3</sub>OH); MS (ES) m/e 394.2 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub> · 2 TFA · 0.125 H<sub>2</sub>O: C, 46.22; H, 3.43; N, 11.23. Found: C, 46.13; H, 3.78; N, 11.49.

#### Example 39

25 Preparation of (±)-N-[2-(aminomethyl)-4-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]aspartic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

EDC (130 mg, 0.75 mmol) was added to a solution of methyl (±)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-1H-1,4-benzodiazepine-2-acetate (190 mg, 0.68 mmol), 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride (169 mg, 0.68 mmol), HOBt · H<sub>2</sub>O (101 mg, 0.75 mmol), and DIEA (0.39 mL, 2.24 mmol) in anhydrous DMF at RT. After 20 hr, the reaction was concentrated on the rotavap (high vacuum), and the residue was chromatographed on silica gel (1 - 6.5% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound (260 mg, 88%) as a white solid: MS (ES) m/e 437.5 (M + H)<sup>+</sup>.

b) (±)-N-[2-(Aminomethyl)-4-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]aspartic acid

- Following the procedure of Example 37(f), except substituting methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate for methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate, the title compound (66%) was prepared as a white powder: MS (ES) m/e 441.2 (M + H)<sup>+</sup>.  
 10 Anal. Calcd for C<sub>21</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub> · 2 TFA · 2.25 H<sub>2</sub>O: C, 42.08; H, 4.38; N, 11.78. Found: C, 42.01; H, 4.18; N, 11.55.

#### Example 40

- 15 Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

- 20 Following the procedure of Example 38(b), except substituting 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride for 2-aminomethylbenzimidazole dihydrochloride hydrate, the title compound (63%) was prepared as an amber solid: MS (ES) m/e 423 (M + H)<sup>+</sup>.

- 25 b) (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

- Following the procedure of Example 37(f), except substituting methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate for methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate, the title compound (50%) was prepared as a white powder: MS (ES) m/e 409.2 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>6</sub>O<sub>4</sub> · 1.75 TFA · H<sub>2</sub>O: C, 45.09; H, 3.82; N, 13.45. Found: C, 45.18; H, 4.10; N, 13.58.

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#### Example 41

Preparation of (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate

5 a) tert-Butyl 4-fluoro-3-[[2-(pyrid-3-yl)ethyl]amino]benzoate

A mixture of tert-butyl 4-fluoro-3-methylbenzoate (3.83 g, 18.22 mmole), NBS (3.57 g, 20.24 mmole), benzoyl peroxide (0.22 g, 0.91 mmole), and CCl<sub>4</sub> (90 mL) was heated at reflux. After 16 hr, the reaction was cooled in ice/H<sub>2</sub>O and filtered, and the filtrate was concentrated. The residue was passed through a short  
10 pad of silica gel (20 % EtOAc/hexane) to remove baseline materials, and the filtrate was concentrated. The residue was dissolved in THF (90 mL), and 3-(2-aminoethyl)pyridine (6.97 g, 57 mmol) was added rapidly. The addition appeared to be mildly endothermic. The reaction was stirred overnight then was concentrated. The residue was diluted with Et<sub>2</sub>O (100 mL) and washed sequentially with 1.0 N  
15 NaOH (30 mL), H<sub>2</sub>O (30 mL), and brine (30 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (2.58 g, 59 %) as a yellow oil: MS (ES) m/e 331 (M + H)<sup>+</sup>.

20 b) tert-Butyl (S)-4-fluoro-3-[2-aza-4-(benzyloxycarbonyl)amino-3,6-dioxo-6-methoxy-2-[2-(pyrid-3-yl)ethyl]hexyl]benzoate

DCC (1.86 g, 9 mmol) was added to a solution of tert-butyl 4-fluoro-3-[[2-(pyrid-3-yl)ethyl]amino]benzoate (2.7 g, 8.18 mmol), N-Cbz-L-aspartic acid β-methyl ester (*J. Am. Chem. Soc.* 1957, 79, 5697; 2.53 g, 9 mmol), and HOBt · H<sub>2</sub>O (1.2 g, 9 mmol) in anhydrous DMF (10 mL) at RT. After 24 hr, the mixture was  
25 diluted with Et<sub>2</sub>O (25 mL) and filtered. The filtrate was concentrated to dryness, and the residue was diluted with Et<sub>2</sub>O (50 mL) and washed with H<sub>2</sub>O (2 x 10 mL) and brine (10 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound (2.4 g, 49%) as a colorless oil: MS (ES) m/e 594 (M + H)<sup>+</sup>.

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c) tert-Butyl (S)-4-fluoro-3-[4-amino-2-aza-3,6-dioxo-6-methoxy-2-[2-(pyrid-3-yl)ethyl]hexyl]benzoate

A mixture of tert-butyl (S)-4-fluoro-3-[2-aza-4-(benzyloxycarbonyl)amino-3,6-dioxo-6-methoxy-2-[2-(pyrid-3-yl)ethyl]hexyl]benzoate (2.4 g, 4 mmol), 10 %  
35 Pd/C (184 mg, 0.17 mmole), and MeOH (17 mL) was shaken at RT under H<sub>2</sub> (50 psi). After 1.5 hr, the reaction was filtered through celite® and concentrated. Silica



gel chromatography (10 % MeOH in 1:1 EtOAc/CHCl<sub>3</sub>) gave the title compound (1.1 g, 59 %) as a colorless oil: MS (ES) 460 (M + H)<sup>+</sup>.

- d) Methyl (S)-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-4-[2-(pyrid-3-yl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

A solution of tert-butyl (S)-4-fluoro-3-[4-amino-2-aza-3,6-dioxo-6-methoxy-2-[2-(pyrid-3-yl)ethyl]hexyl]benzoate (0.64 g 1.39 mmol) in anhydrous DMSO (5.7 mL) was heated under argon in an oil bath set at 120-125°C. After 17.5 hr, the reaction was cooled in ice/H<sub>2</sub>O and diluted with H<sub>2</sub>O (12 mL). The mixture was extracted with EtOAc (3 x 20 mL), and the combined EtOAc layers were washed with H<sub>2</sub>O (10 mL) and brine (10 mL). Drying (MgSO<sub>4</sub>), concentration, and silica gel chromatography (9:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) gave the title compound (0.15 g, 33%) as a nearly colorless solid: MS (ES) m/e 440 (M + H)<sup>+</sup>.

- e) Methyl (S)-2,3,4,5-tetrahydro-7-carboxy-4-[2-(pyrid-3-yl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

4 M HCl/dioxane (0.5 mL) was added to a solution of methyl (S)-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-4-[2-(pyrid-3-yl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.18 g, 4.1 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the reaction was stirred at RT overnight. Concentration in vacuo followed by reconcentration from toluene (3 x 10 mL) gave the title compound (0.12 g, 65%): MS (ES) m/e 384 (M + H)<sup>+</sup>.

- f) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate

A mixture of methyl (S)-2,3,4,5-tetrahydro-7-carboxy-4-[2-(pyrid-3-yl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.12 g, 0.26 mmol) and thionyl chloride (15 mL) was refluxed for 1 h. The resulting orange solution was concentrated to dryness to leave a yellow-orange foam. This was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and added dropwise to a solution containing 2-aminomethylbenzimidazole dihydrochloride hydrate (0.058 g, 0.26 mmol), pyridine (0.72 g, 9.1 mmol), and triethylamine (0.55 g, 5.46 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0°C under argon. The reaction mixture was then stirred in RT under argon. After 25.5 h, CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and 5% NaHCO<sub>3</sub> (50 mL) were added to the reaction mixture to give a light yellow precipitate which was filtered and air-dried to give the title compound (0.030 g, 22% yield): MS (ES) m/e 513 (M+H)<sup>+</sup>.

g) (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate

- 1.0 N LiOH (0.57 mL, 0.57 mmol) was added dropwise at RT to a mixture of methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate (0.030 g, 0.059 mmol) in THF (4 mL) and H<sub>2</sub>O (5 mL). The resulting light brownish-yellow solution was stirred for 21.5 h, then was concentrated on the rotavap. The resulting residue was lyophilized to give the crude product as a yellowish powder. Preparative HPLC (PRP-1@ column, step gradient, 10-20% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) afforded the title compound (0.010g 34% yield): MS (ES) m/e 499(M+H)<sup>+</sup>. Anal. Calcd. for C<sub>27</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub> · 3 C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub> · 3 HCl · 3 H<sub>2</sub>O: C, 37.41; H, 3.41; N, 7.52. Found: C, 37.6; H, 3.52; N, 7.52.

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Example 42

Preparation of Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

- a) Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate
- HCl gas was bubbled into EtOH (200 mL) for 10 min, then (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid (2.00 g, 4.5 mmol) was added. The reaction was stirred at RT for 24 hr, then was concentrated to dryness on the rotavap. The residue was reconcentrated from toluene (2 x) to remove residual EtOH, then was chromatographed on silica gel (gradient: 7% MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1 L) then 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The resulting residue was dissolved in EtOH, and Et<sub>2</sub>O was added to precipitate a solid. This was collected and washed with Et<sub>2</sub>O to afford the title compound as a white solid: MS (ES) m/e 450.2 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>24</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> · 1.5 H<sub>2</sub>O: C, 60.49; H, 6.35; N, 14.70. Found: C, 60.41; H, 6.27; N, 14.38.

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Example 43

Preparation of 4-[[[3-(1H-benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetic acid

## a) 2-[3-(N-tert-Butoxycarbonyl)aminopropyl]benzimidazole

A solution of isobutylchloroformate (10.2 mL, 79 mmol) in THF (25 mL) was added to a solution of 4-(tert-butoxycarbonyl)aminobutyric acid (*Organic*  
5 *Synthesis* 1984, 63, 160; 13.5 g, 0.066 mole) and triethylamine (11 mL, 80 mmol) in THF (50 mL) at 0°C under argon. After 0.5 h, a solution of 1,2-phenylenediamine (7 g, 64.8 mmole) in THF (50 mL) was added dropwise to the resulting white suspension. The reaction was stirred for 18 h, then was filtered, and the filtrate was concentrated to give a semi-solid. This was dissolved in AcOH (100 mL), and the  
10 solution was heated at 70°C for 18 h. The reaction mixture was concentrated, and the residue was reconcentrated several times from toluene. Silica gel flash chromatography gave the title compound (6.0 g, 33%): MS (ES) m/e 276 [M+H]<sup>+</sup>.

## b) 2-(3-Aminopropyl)benzimidazole dihydrochloride

15 A solution of 2-[3-(N-tert-butoxycarbonyl)aminopropyl]benzimidazole (1.2 g, 4.3 mmol) and 4 M HCl in dioxane (20 mL) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was stirred at RT for 18 h. The resulting white suspension was filtered to give the title compound (1.07 g, 97%).

## c) Ethyl 4-[[[3-(1H-benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetate

A mixture of ethyl 4-carboxypiperidine-1-acetate hydrochloride (Yellin's SB 223913 CIP)(0.76 g, 3 mmol) in thionyl chloride (10 mL) was heated to reflux for 15 min, then was concentrated to dryness. After evaporation several times from toluene, the residue was dissolved with 2-(3-aminopropyl)benzimidazole  
25 dihydrochloride (0.77 g, 3 mmol) and DIEA (3 mL) in DMF (25 mL). After 18 h, the reaction mixture was partitioned between EtOAc (50 mL) and 5% NaHCO<sub>3</sub> (100 mL), and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed sequentially with H<sub>2</sub>O and saturated NaCl solution, then were dried over MgSO<sub>4</sub>. Concentration and silica gel flash chromatography (6% MeOH/CH<sub>2</sub>Cl<sub>2</sub>)  
30 gave the title compound (40 mg, 3%).

## b) 4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetic acid

1N NaOH solution (0.4 mL, 0.4 mmol) was added to a stirred solution of ethyl 4-[[[3-(1H-benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetate (40  
35 mg, 0.1 mmol) in MeOH (10 mL) at RT. After 18 h, the mixture was neutralized with AcOH (1 mL) and concentrated to remove the MeOH. The aqueous solution was loaded onto an XAD-2 column, and eluted with H<sub>2</sub>O (500 mL), then with 20%

CH<sub>3</sub>CN/ H<sub>2</sub>O. The fractions containing the product were pooled and lyophilized to give the title compound (9 mg, 25%). MS (ES) m/e 345.2 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub> · 0.75 H<sub>2</sub>O: C, 60.40; H, 7.18; N, 15.65. Found: C, 60.48; H, 7.16; N, 15.40.

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Example 44Preparation of 4-[[[3-(benzimidazol-2-yl)propyl]amino]carbonyl]phenylacetic acid

- 10 a) Ethyl 4-[[[3-(benzimidazol-2-yl)propyl]amino]carbonyl]-1-phenylacetate  
A mixture of ethyl 2-(4-carboxyphenyl)acetate (Yellin's SB 223913 CIP)(0.5 g, 2.4 mmol), 2-(3-aminopropyl)benzimidazole dihydrochloride (0.7 g, 2.8 mmol), HOBt · H<sub>2</sub>O (0.36 g, 2.6 mmol), EDC (0.5 g, 2.6 mmol), and DIEA (1.5 mL, 8.8 mmol) in DMF (15 mL) was warmed briefly and stirred at RT for 18 h. The reaction mixture was partitioned between EtOAc (50 mL) and 5% NaHCO<sub>3</sub> (100 mL), and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed sequentially with H<sub>2</sub>O and saturated NaCl solution, then were dried over MgSO<sub>4</sub>. The evaporated residual solid was triturated with Et<sub>2</sub>O to give the title compound (0.56 g, 66%): MS (ES) m/e 366.0[M+H]<sup>+</sup>. Anal. Calcd for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub> · 0.25 H<sub>2</sub>O: C, 68.18; H, 6.40; N, 11.36. Found: C, 68.16; H, 6.26; N, 11.36.

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- b) 4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]phenylacetic acid  
1 N NaOH solution (6 mL, 6 mmol) was added to a stirred solution of ethyl 4-[[[3-(1H-benzimidazol-2-yl)propyl]amino]carbonyl]-1-phenylacetate (0.38 g, 1 mmol) in MeOH (15 mL) at RT. After 4 h, the mixture was neutralized with AcOH (6 mL) and the resulting solid was filtered to give the title compound (77 mg, 22%): MP 108-110°C; MS (ES) m/e 345.2 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>11</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub> · 0.6 H<sub>2</sub>O: C, 65.54; H, 5.85; N, 12.07. Found: C, 65.63; H, 5.65; N, 11.95.

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Example 45Preparation of (S)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[5-trifluoromethyl]benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid

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- a) 3,4-Diaminobenzotrifluoride

4-Amino-3-nitrobenzotrifluoride (3.7070 g, 17.98 mmol) was dissolved in MeOH, and a catalytic amount of 10% Pd/C was added. The reaction was purged with H<sub>2</sub>, and stirred at RT under H<sub>2</sub> (balloon). After 24 hr, the reaction was filtered through a bed of celite®, and the filtrate was evaporated under vacuum to yield the title compound (3.0878 g, 98%). The material was used without characterization.

b) 2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-5-trifluoromethylbenzimidazole

Cbz-sarcosine (3.9950 g, 17.13 mmol) was dissolved in dry THF, and isobutylchloroformate (2.5 mL, 19.27 mmol) was added, followed by triethylamine (5.0 mL, 35.95 mmol). The mixed anhydride was allowed to form at RT for 30 min, then was added to a solution of 3,4-diaminobenzotrifluoride (3.0818 g, 7.53 mmol) in dry THF. After 20 hours at RT, the reaction was evaporated under vacuum. The residue was partitioned between EtOAc and 1.0 N NaHCO<sub>3</sub>, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried (MgSO<sub>4</sub>), filtered and evaporated under vacuum. The residue was reconcentrated from toluene, then was dissolved in glacial AcOH (125 mL). The solution was heated at 110°C for 24 hr, then the AcOH was evaporated under vacuum. The residue was reconcentrated from toluene, then was adsorbed onto silica gel and loaded onto a dry silica gel flash chromatography column. The column was eluted with 1:1 CHCl<sub>3</sub>/Et<sub>2</sub>O to afford the title compound (2.9397 g, 47.2%): TLC R<sub>f</sub> (1:1 CHCl<sub>3</sub>/Et<sub>2</sub>O) 0.57; MS (ES) m/e 364.2 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.0 - 7.2 (m, 9H), 5.05 (s, 2H), 4.84 (s, 2H), 3.07 (s, 3H).

c) 2-(Methylaminomethyl)-5-trifluoromethylbenzimidazole

2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-5-trifluoromethylbenzimidazole (2.9397 g, 8.09 mmol) was dissolved in MeOH, and a catalytic amount of 10% Pd/C was added. The reaction was purged with H<sub>2</sub>, then was stirred at RT under H<sub>2</sub>. After 5 hr, the reaction mixture was filtered through a bed of celite®, and the filtrate was evaporated under vacuum to leave a tan colored oil. Analysis by 400 MHz NMR showed the Cbz protecting group was still present, so the residue was resubmitted to the reaction conditions. After 18 hr, the catalyst was removed by filtration through a bed of celite® and the filtrate was evaporated under vacuum to yield the title compound (1.7809 g, 96%): <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.76 - 7.32 (m, 4H), 4.32 (s, 2H), 2.59 (s, 3H).

d) Methyl (S)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (179.2 mg, 0.61 mmol) was weighed into a 100 mL round bottomed flask. CH<sub>3</sub>CN (10 mL) was added, followed by HOBt · H<sub>2</sub>O (97.9 mg, 0.72 mmol) and EDC (149.3 mg, 0.78 mmol). After all the solids had dissolved, a solution of 2-(methylaminomethyl)-5-trifluoromethylbenzimidazole (186.1 mg, 0.81 mmol) in CH<sub>3</sub>CN was added with diisopropylethylamine (0.25 mL, 1.44 mmol). After 24 hr at RT, the reaction was evaporated under vacuum, and the residue was chromatographed on silica gel (3% MeOH/CHCl<sub>3</sub>) to afford the title compound (308.1 mg, 100%): TLC R<sub>f</sub> (5% MeOH/CHCl<sub>3</sub>) 0.21; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.83-7.16 (m, 7H), 5.37 (d, 1H), 5.05-4.70 (m, 3H), 2.96 (m, 3H), 3.72 (s, 3H), 3.16 (s, 2H), 2.11 (s, 3H); MS (ES) m/e 504.0 (M+H)<sup>+</sup>.

e) (S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid

Methyl (S)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetate (308.1 mg, 0.61 mmol) was dissolved in MeOH (5 mL). H<sub>2</sub>O (5 mL) was added, followed by 1.0 N NaOH (2.0 mL, 2.0 mmol). After 24 hr at RT, the reaction was neutralized with 1.0 N HCl (2.0 mL). The milky white mixture was stirred at RT for 15 min, then was diluted with H<sub>2</sub>O, and the precipitate was collected on a sintered glass funnel. The white powder was dried in a vacuum desiccator overnight to yield the title compound (268.0 mg, 90%): MS (ES) m/e 490.2 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>F<sub>3</sub> · 2.25 H<sub>2</sub>O · 0.25 HCl: C, 51.24; H, 5.00; N, 12.99. Found: C, 51.44; H, 4.96; N, 12.45.

#### Example 46

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole

Following the procedure of Example 45(b), except substituting 1,2-diamino-3,6-dimethoxybenzene for the 3,4-diaminobenzotrifluoride, the title compound was

prepared: MS (ES) m/e 356.2 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.34 (s, 5H), 6.54 (d, 2H), 5.18 (s, 2H), 4.65 (s, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.03 (s, 3H).

5 b) 4,7-Dimethoxy-2-(methylaminomethyl)benzimidazole

2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole (186.5 mg, 0.53 mmol) was dissolved in MeOH, and a catalytic amount of 10% Pd/C was added. The reaction was purged with H<sub>2</sub>, then was stirred at RT under H<sub>2</sub> (balloon). After 20 hr, the reaction was filtered through  
10 celite®, and the filtrate was evaporated under vacuum to yield the title compound (96.9 mg, 83%): <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 6.52 (s, 2H), 3.94-3.86 (m, 6H), 2.36 (s, 3H).

c) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate  
15 Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (112.3 mg, 0.38 mmol) was weighed into a 100 mL round bottomed flask. CH<sub>3</sub>CN was added, followed by HOBt · H<sub>2</sub>O (62.3 mg, 0.46 mmol) and EDC (120.0 mg, 0.63 mmol). When the solids had all dissolved,  
20 diisopropylethylamine (0.1 mL, 0.57 mmol) was added, followed by a suspension of 4,7-dimethoxy-2-(methylaminomethyl)benzimidazole (96.8 mg, 0.44 mmol) in CH<sub>3</sub>CN containing diisopropylethylamine (0.1 mL, 0.57 mmol). After 2.5 days at RT, the reaction was evaporated under vacuum. The residue was evaporated once with toluene, then was chromatographed on silica gel (CHCl<sub>3</sub>, then 5%  
25 MeOH/CHCl<sub>3</sub>) to afford the title compound (152.0 mg, 80.0%): TLC R<sub>f</sub> (5% MeOH/CHCl<sub>3</sub>) 0.35; MS (ES) m/e 496.2 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.25 (m, 2H), 6.56 (s, 2H), 5.36 (d, 1H), 3.91 (s, 6H), 3.70 (s, 3H), 3.08 (s, 3H).

d) (S)-2,3,4,5-Tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid  
30

Following the procedure of Example 45(e), methyl (S)-2,3,4,5-tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound  
35 (110.0 mg, 74%): MS (ES) m/e 482.2 (M+H)<sup>+</sup>. Anal Calcd for C<sub>24</sub>H<sub>27</sub>N<sub>3</sub>O<sub>6</sub> · 0.75 H<sub>2</sub>O: C, 58.23; H, 5.80; N, 14.15. Found: C, 58.26; H, 5.59; N, 13.90.

Example 47

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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## a) 1,2-Diamino-3-methylbenzene

Following the procedure of Example 45(a), except substituting 2-methyl-6-nitroaniline (3.0204 g, 19.98 mmol) for the 4-amino-3-nitrobenzotrifluoride, the title compound (2.4815 g) was prepared. This was used without characterization.

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## b) 2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-4-methylbenzimidazole

Cbz-sarcosine (4.6466 g, 19.92 mmol) was dissolved in dry THF in a 100 mL round-bottomed flask. Triethylamine (3.0 mL, 21.57 mmol) was added, followed by isobutylchloroformate (2.8 mL, 21.59 mmol). The white reaction mixture was stirred at RT for 0.5 hr, then was added to a solution of 1,2-diamino-3-methylbenzene (2.4815 g) in dry THF at -20 to -30°C. After 20 min, the reaction was warmed to RT and stirred there for 16 hr. The reaction was evaporated under vacuum and the residue was partitioned between EtOAc and 1.0 N NaHCO<sub>3</sub>. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried (MgSO<sub>4</sub>), filtered, and evaporated under vacuum. The residue was reconcentrated from toluene and the dried solid was dissolved in glacial AcOH (150 mL). The solution was heated at 110°C for 18 hr, then was concentrated under high vacuum. The residue was reconcentrated from toluene, then was adsorbed onto silica gel and loaded onto a dry silica gel flash chromatography column. The column was eluted with 1:1 CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O to afford the title compound (3.1586 g, 51%): MS (ES) m/e 310.2 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.35-7.01 (m, 10H), 5.00 (s, 2H), 4.72 (s, 2H), 2.99 (s, 3H), 2.55 (s, 3H).

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## c) 4-Methyl-2-(methylaminomethyl)benzimidazole

Following the procedure of Example 45(c), except substituting 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-4-methylbenzimidazole for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5-trifluoromethylbenzimidazole, the title compound (2.9916 g, quantitative) was prepared: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.36-7.01 (m, 4H), 4.01 (s, 2H), 2.52 (s, 3H), 2.41 (s, 3H).

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## d) Methyl (S)-2,3,4,5-tetrahydro-7-[[[4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate



Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (188.5 mg, 0.64 mmol) was weighed into a 100 mL round bottomed flask. CH<sub>3</sub>CN was added, followed, sequentially, by HOBt · H<sub>2</sub>O (103.5 mg, 0.77 mmol), EDC (149.3 mg, 0.78 mmol), and diisopropylethylamine (0.15 mL, 0.86 mmol). After 15 min, a solution of 4-methyl-2-(methylaminomethyl)benzimidazole (273.8 mg, 1.56 mmol) in CH<sub>3</sub>CN was added. CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added to dissolve some material. After 18 hr at RT, the reaction was concentrated, and the residue was chromatographed on silica gel (5% MeOH/CHCl<sub>3</sub>) to afford the title compound (307.3 mg, quantitative): MS (ES) m/e 450.2 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.23-7.03 (m, 7H), 6.41 (br s, 1H), 5.33 (d, J = 16.3 Hz, 1H), 3.69 (s, 3H), 3.46 (s, 3H), 3.10 (s, 3H).

e) (S)-2,3,4,5-Tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 45(e), methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (307.3 mg, 0.68 mmol) was saponified to afford the title compound (243.9 mg, 82%): MS (ES) m/e 436.2 (M+H)<sup>+</sup>. Anal Calcd for C<sub>23</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub> · 2.75 H<sub>2</sub>O: C, 56.96; H, 6.34; N, 14.44: Found: C, 56.72; H, 6.27; N, 14.26.

#### Example 48

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 2-Amino-4,6-dimethyl-3-nitropyridine

2-Amino-4,6-dimethylpyridine (5.55 g, 45.43 mmol) was weighed into a 500 mL round bottomed flask. The flask was cooled to -78°C. Concentrated H<sub>2</sub>SO<sub>4</sub> (25 mL, 450 mmol) was added, followed by concentrated HNO<sub>3</sub> (3.5 mL, 56.0 mmol). The mixture became a solid frozen mass. The cooling bath was removed and the reaction was allowed to warm to RT. After about 15 min there was an exothermic reaction with the release of some nitrous oxide gas, and the reaction became a very dark red color. The reaction was heated at 85 - 90°C for 3 hr, then was cooled to RT, diluted with ice, and neutralized with 6 N NaOH (160 mL). The aqueous solution was extracted with EtOAc (3 x), and the combined EtOAc layers were dried

(MgSO<sub>4</sub>), filtered, and evaporated under vacuum. The resulting yellowish-orange solid was adsorbed onto silica gel and flash chromatographed on a dry silica gel column. The column was eluted with 1:1 CHCl<sub>3</sub>/Et<sub>2</sub>O to afford the title compound (1.0650 g, 14%): MS (ES) m/e 168.0 (M+H)<sup>+</sup>.

5

b) 2,3-Diamino-4,6-dimethylpyridine

Following the procedure of Example 45(a), except substituting 2-amino-4,6-dimethyl-3-nitropyridine (1.0650 g, 6.37 mmol) for the 4-amino-3-nitrobenzotrifluoride, the title compound (836.1 mg, 95.7%) was prepared. This was used without characterization.

10

c) 4-Aza-2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5,7-dimethylbenzimidazole

Following the procedure of Example 45(b), except substituting 2,3-diamino-4,6-dimethylpyridine (836.1 mg, 6.09 mmol) for the 3,4-diaminobenzotrifluoride, the title compound (1.2273 g, 62%) following silica gel chromatography (3% MeOH/CHCl<sub>3</sub>): MS (ES) m/e 325.0 (M+H)<sup>+</sup>.

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d) 4-Aza-2-(methylaminomethyl)-5,7-dimethylbenzimidazole

Following the procedure of Example 45(c), except substituting 4-aza-2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5,7-dimethylbenzimidazole (1.2273 g, 3.78 mmol) for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5-trifluoromethylbenzimidazole, the title compound was obtained as a white powder following trituration with Et<sub>2</sub>O. This material was used without characterization.

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e) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (175.0 mg, 0.60 mmol) was weighed into a 100 mL round bottomed flask. CH<sub>3</sub>CN (10 mL) was added, followed sequentially, by HOBT · H<sub>2</sub>O (115.9 mg, 0.86 mmol), EDC (124.9 mg, 0.65 mmol), and diisopropylethylamine (0.13 mL, 0.75 mmol). A suspension of 4-aza-2-(methylaminomethyl)-5,7-dimethylbenzimidazole (144.5 mg, 0.76 mmol) and diisopropylethylamine (0.13 mL, 0.75 mmol) in CH<sub>3</sub>CN was added, and the reaction was stirred at RT. After 22 hr, the reaction was evaporated under vacuum, and the residue was co-evaporated with toluene. Silica gel chromatography (3% MeOH/CHCl<sub>3</sub>, (1 L) then 5%

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MeOH/CHCl<sub>3</sub>) gave the title compound (76.9 mg, 28%): MS (ES) m/e 465.2 (M+H)<sup>+</sup>.

- f) (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid
- Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (76.9 mg, 0.17 mmol) was dissolved in MeOH (5 mL) and H<sub>2</sub>O (5 mL), and 1.0 N NaOH (0.5 mL, 0.5 mmol) was added. After 24 hours at RT, the reaction was neutralized with 1.0 N HCl (0.5 mL), and the solvents were evaporated under vacuum. ODS chromatography (gradient: 5% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 10% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 15% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 30% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL)) gave a residue which was co-evaporated once with toluene and dried under high vacuum. The resulting residue was dissolved in MeOH (5 mL) and precipitated with Et<sub>2</sub>O. The white solid was collected on a sintered glass funnel and dried in a vacuum desiccator overnight to yield the title compound (52.0 mg, 68%): HPLC (ODS column, 1.5 mL/min; gradient 5-50% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA) t<sub>r</sub> 12.38 min; MS (ES) m/e 451.2 (M+H)<sup>+</sup>. Anal Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>6</sub>O<sub>4</sub> · 1 H<sub>2</sub>O · 1 CF<sub>3</sub>CO<sub>2</sub>H: C, 51.55; H, 5.02; N, 14.43: Found: C, 51.34; H, 5.00; N, 14.41.

#### Example 49

- 25 Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

##### a) 1,2-Diamino-4,5-difluorobenzene

- 30 Following the procedure of Example 45(a), except substituting 4,5-difluoro-2-nitroaniline (2.0 g, 11.49 mmol) for the 4-amino-3-nitrobenzotrifluoride, the title compound was prepared. This was used without characterization.

##### b) 2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-5,6-difluorobenzimidazole

- 35 Following the procedure of Example 47(b), except substituting 1,2-diamino-4,5-difluorobenzene for the 1,2-diamino-3-methylbenzene, and running the AcOH cyclization step at 80°C instead of at 110°C, the title compound (1.3767 g, 36%) was

prepared: TLC Rf (1:1 CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O) 0.42; MS (ES) m/e 332.0 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.50-7.14 (m, 8H), 5.13 (s, 2H), 4.61 (s, 2H), 3.06 (s, 3H).

5 c) 5,6-Difluoro-2-(methylaminomethyl)benzimidazole

Following the procedure of Example 46(b), except substituting 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5,6-difluorobenzimidazole (1.3767 g, 4.16 mmol) for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole, the title compound (875.6 mg, quantitative) was prepared:

10 MS (ES) m/e 198.0 (M+H)<sup>+</sup>.

d) Methyl-(S)-2,3,4,5-tetrahydro-7-[[[5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate  
Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-

15 benzodiazepine-2-acetate (415.7 mg, 1.42 mmol) was taken up in CH<sub>3</sub>CN, and HOBt · H<sub>2</sub>O (209.3 mg, 1.55 mmol) and EDC (314.9 mg, 1.64 mmol) were added. After 5 min, and diisopropylethylamine (0.25 mL, 1.64 mmol) was added, which produced a clear, colorless solution. A solution of 5,6-difluoro-2-

(methylaminomethyl)benzimidazole (284.5 mg, 1.44 mmol) in CH<sub>3</sub>CN was added.  
20 After 30 minutes, the reaction became slightly turbid, so more diisopropylethylamine (0.25 mL) was added, which made the reaction again clear and colorless. After 24 hr, the reaction was evaporated under vacuum. The residue was co-evaporated once with toluene, then was chromatographed on silica gel (CHCl<sub>3</sub>, 0.25 L), then 2% MeOH/CHCl<sub>3</sub> (1.5 L), then 5% MeOH/CHCl<sub>3</sub> to afford  
25 the title compound (456.8 mg, 68%): MS (ES) m/e 472.2 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.34-7.08 (m, 6H), 6.44 (br s, 1H), 5.39 (d, J = 16.2 Hz, 1H), 3.70 (s, 3H), 3.14 (s, 3H), 2.96 (s, 3H).

e) (S)-2,3,4,5-Tetrahydro-7-[[[5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Methyl (S)-2,3,4,5-tetrahydro-7-[[[5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (456.8 mg, 0.97 mmol) was dissolved in MeOH (10 mL) and H<sub>2</sub>O (10 mL). 1.0 N  
35 NaOH (3.0 mL, 3.0 mmol) was added and the reaction was stirred at RT. After 18 hr, the reaction was neutralized with 1.0 N HCl (3.0 mL). A white precipitate formed which was collected on a sintered glass filter and dried in a vacuum

desiccator. ODS chromatography (gradient: 10% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 18% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 25% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL)) gave a residue which was co-evaporated once with toluene. The resulting residue was dissolved in a small amount of MeOH and precipitated with Et<sub>2</sub>O to give the title compound (330.9 mg) as a white powder: HPLC (ODS column; 1.5 mL/min; gradient 5-50% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA)  $t_r$  = 14.12 min; MS (ES)  $m/e$  458.2 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>F<sub>2</sub> · 2.5 H<sub>2</sub>O: C, 52.57; H, 5.22; N, 13.94: Found: C, 52.76; H, 5.15; N, 13.67.

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### Example 50

#### Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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a) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (228.8 mg, 0.78 mmol) was taken up in CH<sub>3</sub>CN, and HOBT · H<sub>2</sub>O (154.2 mg, 1.14 mmol), EDC (179.4 mg, 0.94 mmol), and diisopropylethylamine (0.50 mL, 0.94 mmol) were added sequentially. A solution of 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride (125.4 mg, 0.77 mmol) in CH<sub>3</sub>CN /DMF was added, and the reaction was stirred at RT. After 24 hr, the reaction was evaporated under vacuum, and the residue was co-evaporated once with toluene. Silica gel chromatography (CHCl<sub>3</sub>, (0.25 L) then 3% MeOH/CHCl<sub>3</sub>, (0.5 L), then 5% MeOH/CHCl<sub>3</sub>) gave the title compound (159.9 mg, 48%): MS (ES)  $m/e$  437.2 (M+H)<sup>+</sup>.

25

b) (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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Following the procedure of Example 48(f), methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (159.9 mg, 0.37 mmol) was saponified and purified to afford the title compound: MS (ES)  $m/e$  423.39 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>21</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub> · 0.5 H<sub>2</sub>O · 1.25 TFA: C, 52.64; H, 5.02; N, 16.74. Found: C, 52.65; H, 5.02; N, 16.74.

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Example 51Preparation of (S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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## a) 2-[N-(tert-Butoxycarbonyl)-N-methyl]aminomethyl-4-nitrobenzimidazole

Boc-sarcosine (2.0320 g, 10.74 mmol) was dissolved in dry THF and cooled in a dry-ice/acetone bath to -15°C. Triethylamine (5.0 mL, 3.6375 mmol) was added, followed by isobutylchloroformate (1.5 mL, 11.56 mmol). After 0.5 hr, the mixture was added to a solution of 1,2-diamino-3-nitrobenzene (1.3047 g, 10.77 mmol) in dry THF at -20°C, and the reaction was allowed to warm to RT. After 24 hr, the reaction was evaporated under vacuum and the residue was partitioned between EtOAc and 1.0 N NaHCO<sub>3</sub>. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried (MgSO<sub>4</sub>), filtered, and evaporated under vacuum. The residue was dissolved in glacial AcOH (100 mL), and the solution was heated at 75°C. After 24 hr, the reaction was evaporated under vacuum, and the residue was co-evaporated with toluene (2 x). The material was adsorbed onto silica gel and flash chromatographed on a dry silica gel column (gradient: CHCl<sub>3</sub> (0.5 L), then 2% MeOH/CHCl<sub>3</sub> (1 L), then 5% MeOH/CHCl<sub>3</sub>) to afford the title compound (2.2089 g, 75%): <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.10 (dd, 2H), 7.40-7.32 (m, 1H), 4.69 (s, 2H), 3.02 (s, 3H), 1.54 (s, 9H).

## b) 2-(Methylaminomethyl)-4-nitrobenzimidazole

2-[N-(tert-Butoxycarbonyl)-N-methyl]aminomethyl-4-nitrobenzimidazole (2.2089 g, 8.05 mmol) was treated with 4 N HCl in dioxane at RT. After the addition, there was an immediate precipitation of a white solid. After 4 hr, the reaction was evaporated under vacuum and the residue was triturated with diethyl ether to give the title compound (1.639 g) as a white solid. This was used without characterization.

30

## c) Methyl-(S)-2,3,4,5-tetrahydro-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 49(d), except substituting 2-(methylaminomethyl)-4-nitrobenzimidazole for 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (292.9 mg, quantitative) was prepared: MS(ES) m/e 481.2 (M+H)<sup>+</sup>.

35

d) (S)-2,3,4,5-Tetrahydro-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 45(e), methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (292.9 mg, 0.61 mmol) was saponified to afford the title compound (211.0 mg, 68%): MS (ES) m/e 467.4 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>22</sub>N<sub>6</sub>O<sub>6</sub> · 2.5 H<sub>2</sub>O: C, 52.12; H, 5.27; N, 16.58: Found: C, 52.07; H, 4.97; N, 16.40.

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### Example 52

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-aminobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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a) (S)-2,3,4,5-tetrahydro-7-[[[(4-aminobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

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(S)-2,3,4,5-Tetrahydro-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid (108.7 mg, 0.21 mmol) was dissolved in MeOH, and a catalytic amount of 10% Pd/C was added. The reaction was purged with H<sub>2</sub>, then was stirred at RT under H<sub>2</sub> (balloon). After 20 hr, the catalyst was removed by filtration through celite®, and the filtrate was evaporated under vacuum. The resulting solid was dissolved in MeOH, reprecipitated with Et<sub>2</sub>O, dried in a vacuum desiccator, and purified by ODS chromatography (gradient: H<sub>2</sub>O containing 0.1% TFA (500 mL), then 5% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 10% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 15% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 20% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 25% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 30% % CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL)). The resulting material was co-evaporated once with toluene then was triturated with diethyl ether to afford the title compound (34.7 mg): MS (ES) m/e 437.5 (M+H)<sup>+</sup>; Anal. Calcd for C<sub>22</sub>H<sub>24</sub>N<sub>6</sub>O<sub>4</sub> · 1.5 H<sub>2</sub>O · 1.5 TFA: C, 47.32; H, 4.53; N, 13.24: Found: C, 47.35; H, 4.86; N, 13.61.

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### Example 53

Preparation of 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid

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a) 2-[1(R)-[N-(Benzyloxycarbonyl)-N-methyl]aminoethyl]benzimidazole

Following the procedure of Example 47(b), except substituting Cbz-N-methyl-D-alanine for the Cbz-sarcosine, and substituting 1,2-phenylenediamine for the 1,2-diamino-3-methylbenzene, and running the AcOH cyclization step at 80°C instead of at 110°C, the title compound was prepared: MS (ES) m/e 310.2 (M+H)<sup>+</sup>.

10

b) 2-[1(R)-(Methylaminoethyl)]benzimidazole

Following the procedure of Example 46(b), except substituting 2-[1(R)-[N-(benzyloxycarbonyl)-N-methyl]aminoethyl]benzimidazole for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole, the title compound (276.0 mg, 48%) was prepared: MS(ES) m/e 176.2 (M+H)<sup>+</sup>.

15

c) Methyl 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 49(d), except substituting 2-[1(R)-(methylaminoethyl)]benzimidazole for the 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (203.5 mg, 90%) was prepared: MS (ES) m/e 450.5 (M+H)<sup>+</sup>.

20

d) 2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 49(e), methyl 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (179.3 mg, 75%) following ODS chromatography: MS (ES) m/e 436.5 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub> · 0.75 H<sub>2</sub>O · 0.75 TFA: C, 55.01; H, 5.14; N, 13.10; Found: C, 54.98; H, 5.42; N, 12.75.

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Example 54

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Preparation of ethyl (S)-2,3,4,5-tetrahydro-7-[[[(4-Aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

- 5 a) Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(4-Aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate  
(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid  
(0.5 g) was dissolved in EtOH, and the solution was cooled in an ice bath to 0°C.  
10 Gaseous HCl was bubbled into the solution until the solution was saturated, then the flask was sealed with a rubber septum and the cooling bath was removed. The reaction was stirred at RT for 20 hr, then the solvents were evaporated under vacuum. The residue was co-evaporated three times with toluene (3 x), then was dissolved in EtOH and precipitated with Et<sub>2</sub>O. The solid was collected on a sintered  
15 glass funnel and dried in a vacuum desiccator overnight to afford the title compound (483.9 mg): MS (ES) m/e 451.4 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub> · HCl · 1.375 H<sub>2</sub>O: C, 53.98; H, 5.86; N, 16.42. Found: C, 54.00; H, 5.82; N, 16.42.

Example 55

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Preparation of 2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid

- 25 a) 2-[1(S)-[N-(tert-Butoxycarbonyl)-N-methyl]aminoethyl]benzimidazole  
Following the procedure of Example 51(a) except substituting Boc-N-methyl-L-alanine for the Boc-sarcosine, and substituting 1,2-phenylenediamine for the 1,2-diamino-3-nitrobenzene, the title compound (1.7792 g, 65%) was prepared following recrystallization from CHCl<sub>3</sub>/hexanes: MS (ES) m/e 276.4 (M+H)<sup>+</sup>.  
30 b) 2-[1(S)-(Methylaminoethyl)]benzimidazole  
Following the procedure of Example 51(b), except substituting 2-[1(S)-[N-(tert-butoxycarbonyl)-N-methyl]aminoethyl]benzimidazole for the 2-[N-(tert-butoxycarbonyl)-N-methyl]aminomethyl-4-nitrobenzimidazole, the title compound  
35 was prepared. This was used without characterization.

c) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 49(d), except substituting 2-[1(S)-(methylaminoethyl)]benzimidazole for the 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (414.7 mg, 88%) was prepared: MS (ES) m/e 450.2 (M+H)<sup>+</sup>.

d) 2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 45(e), methyl (S)-2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (117.2 mg): MS (ES) m/e 436.2 (M+H)<sup>+</sup>. Anal Calcd for C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub> · 0.75 H<sub>2</sub>O · 0.75 TFA: C, 55.05; H, 5.14; N, 13.10; Found: C, 55.14; H, 5.38; N, 13.04.

#### Example 56

Preparation of 2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid

a) 2-[1(S)-(tert-Butoxycarbonyl)aminoethyl]benzimidazole

Following the procedure of Example 51(a) except substituting Boc-L-alanine for the Boc-sarcosine, and substituting 1,2-phenylenediamine for the 1,2-diamino-3-nitrobenzene, the title compound (714.7 mg, 25%) was prepared: MS (ES) m/e 262.4 (M+H)<sup>+</sup>.

b) 2-[1(S)-(Aminoethyl)]benzimidazole

Following the procedure of Example 51(b), except substituting 2-[1(S)-(tert-butoxycarbonyl)aminoethyl]benzimidazole for the 2-[N-(tert-butoxycarbonyl)-N-methyl]aminomethyl-4-nitrobenzimidazole, the title compound was prepared. This was used without characterization.

c) Methyl 2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 49(d), except substituting 2-[1(S)-(aminoethyl)]benzimidazole for 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (270.7 mg, 80%) was prepared: MS (ES) m/e 436.0 (M+H)<sup>+</sup>.

d) 2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 45(e), methyl 2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (158.1 mg, 61%): MS (ES) m/e 422.0 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub> · 1.75 H<sub>2</sub>O: C, 58.37; H, 5.90; N, 15.46; Found: C 58.17; H, 5.77; N, 15.08.

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**Example 57**

Preparation of 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid

15 a) 2-[1(R)-(Benzyloxycarbonyl)aminoethyl]benzimidazole

Following the procedure of Example 47(b), except substituting Cbz-D-alanine for the Cbz-sarcosine, and substituting 1,2-phenylenediamine for the 1,2-diamino-3-methylbenzene, and running the AcOH cyclization step at 80°C instead of at 110°C, the title compound (1.1455 g, 43%) was prepared: MS (ES) m/e 296.4 (M+H)<sup>+</sup>.

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b) 2-(1(R)-Aminoethyl)benzimidazole

Following the procedure of Example 46(b), except substituting 2-[1(R)-(benzyloxycarbonyl)aminoethyl]benzimidazole for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole, the title compound (258.1 mg, 93%) was prepared: MS(ES) m/e 161.9 (M+H)<sup>+</sup>.

25

c) Methyl 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetate

Following the procedure of Example 49(d), except substituting 2-(1(R)-aminoethyl)benzimidazole for the 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (263.6 mg, 84%) was prepared: MS (ES) m/e 436.3 (M+H)<sup>+</sup>.

30

35 d) 2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 49(e), methyl 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetate was saponified to afford the title compound (125.0 mg, 49%): MS (ES) m/e 422.0 (M+H)<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub> · 0.5 H<sub>2</sub>O · 1.25 HCl: C, 55.51; H, 5.35; N, 14.71. Found: C, 55.70; H, 5.47; N, 14.53.

#### Example 58

##### Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(imidazo[1,2a]pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

###### a) 2-Carboethoxyimidazo[1,2a]pyridine

2-Aminopyridine (4 g, 42.50 mmol) was dissolved in MeOH (50 mL). Ethyl bromopyruvate (8.3 g, 42.50 mmol) was added and the reaction was stirred at 70°C for 2 hr. The solvent was then eliminated and the solution was neutralized with 1 M NaOH. The reaction was extracted with EtOAc, and the combined EtOAc layers were washed with brine. Drying (MgSO<sub>4</sub>), filtration, concentration, and silica gel flash column chromatography (2% MeOH/Cl<sub>2</sub>CH<sub>2</sub>) gave the title compound (4.5 g, 56%) as a pale yellow solid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.43 (t, J = 7 Hz, 3H), 4.45 (q, J = 7 Hz, 2H), 6.86 (t, J = 6.6 Hz, 1H), 7.24 (t, J = 6.6 Hz, 1H).

###### b) 2-Hydroxymethylimidazo[1,2a]pyridine

2-Carboethoxyimidazo[1,2a]pyridine (0.5 g, 2.81 mmol) was dissolved in dry THF at 0°C, and then a solution of lithium aluminum hydride (0.5 mL of a 1.0 M in THF) was added. The reaction was allowed to warm to RT and stirred for 1 hr. H<sub>2</sub>O (0.2 mL) was added, followed by 15% NaOH (0.2 mL), and finally H<sub>2</sub>O (0.6 mL). The solids were removed by filtration and washed with hot THF (2 x 100 mL) and hot CHCl<sub>3</sub> (4 x 100 mL). The filtrate and washings were combined and dried (MgSO<sub>4</sub>). Following filtration the solvents were removed under reduce pressure the residue was purified by silica gel flash column chromatography (5% MeOH/Cl<sub>2</sub>CH<sub>2</sub>) to obtain the title compound (0.1 g, 25%) as pale yellow liquid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.85 (s, 2H), 6.76 (t, J = 6.8 Hz, 1H), 7.15 (t, J = 6.8 Hz, 1H), 7.53 (s, 1H), 7.54 (d, J = 6.7 Hz, 1H), 8.1 (d, J = 6.7 Hz, 1H). MS (ES) m/e 149 (M + H)<sup>+</sup>.

###### c) 2-Chloromethylimidazo[1,2a]pyridine

Thionyl chloride (0.4 mL, 3.2 mmol) was added to a solution of 2-hydroxymethylimidazo[1,2a]pyridine (0.4 g, 2.7 mmol) in  $\text{CHCl}_3$  (30 mL) at  $0^\circ\text{C}$ . After stirring at RT for 1 hr, the suspension was poured into a mixture of ice, 10%  $\text{NaHCO}_3$ , and  $\text{CHCl}_3$ . The layers were separated, and the aqueous phase was  
 5 extracted with  $\text{CHCl}_3$ . The organic extracts were combined and dried ( $\text{MgSO}_4$ ). Following filtration, the solvents were removed under reduce pressure to obtain the title compound (0.4 g, 89%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.7 (s, 2H), 6.7 (t, 1H), 7.2 (t, 1H), 7.5 (d, 1H), 7.6 (s, 1H), 8.0 (d, 1H); MS (ES)  $m/e$  167 ( $\text{M} + \text{H}$ ) $^+$ .

10 d) 2-(Methylaminomethyl)imidazo[1,2a]pyridine

Freshly condensed methylamine (15 mL) was added to a solution of 2-chloromethylimidazo[1,2a]pyridine (317 mg, 2 mmol) in EtOH (5 mL) at  $0^\circ\text{C}$ , and the reaction mixture was allowed to stir at  $0^\circ\text{C}$  for 2 h. The solvent was then eliminated and the residue was purified by reverse-phase column chromatography  
 15 (C-18 silica gel,  $\text{H}_2\text{O}$  containing 0.1 % TFA). Lyophilization gave the title compound (461 mg, 87%) as a white solid:  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  2.5 (s, 3H), 4.0 (s, 2H), 6.7 (t, 1H), 7.2 (t, 1H), 7.5 (d, 1H), 7.6 (s, 1H), 8.1 (d, 1H). MS (ES)  $m/e$  162 ( $\text{M} + \text{H}$ ) $^+$ .

20 e) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (828.2 mg, 2.83 mmol) was taken up in  $\text{CH}_3\text{CN}$ , and  $\text{HOBt} \cdot \text{H}_2\text{O}$  (398.1 mg, 2.92 mmol), EDC (562.9 mg, 2.94 mmol), and  
 25 diisopropylethylamine (1 mL, 5.74 mmol) were added sequentially. When the solids had dissolved, a solution of 2-(methylaminomethyl)imidazo[1,2a]pyridine (460.7 mg, 2.86 mmol) and diisopropylethylamine (1.5 mL, 8.61 mmol) in  $\text{CH}_3\text{CN}$  was added, and the reaction was stirred at RT. After 24 hr, the reaction was concentrated, and the residue was co-evaporated with toluene (2 x). The resulting  
 30 residue was chromatographed on silica gel (5%  $\text{MeOH}/\text{CHCl}_3$ ) to give the title compound (694.6 mg, 56%): MS (ES)  $m/e$  436.4 ( $\text{M} + \text{H}$ ) $^+$ .

f) (S)-2,3,4,5-Tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic  
 35 acid

Methyl (S)-2,3,4,5-tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

(663.4 mg, 1.52 mmol) was dissolved in MeOH (10 mL). H<sub>2</sub>O (10 mL) was added, followed by 1.0 N NaOH (5 mL, 5.0 mmol), and the reaction was stirred at RT. After 20 hr, the reaction was neutralized with 1.0 N HCl (5 mL), and the solution was evaporated under vacuum. The residue was purified by ODS  
5 chromatography (gradient: H<sub>2</sub>O containing 0.1% TFA (500 mL), then 5% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 10% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 15% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL), then 20% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (500 mL)) followed by rechromatography  
10 on ODS (gradient: H<sub>2</sub>O containing 0.1% TFA (250 mL), then 10% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (1.5 L), then 20% CH<sub>3</sub>CN/H<sub>2</sub>O containing 0.1% TFA (1 L). Fractions containing pure material were combined and concentrated. The residue was co-evaporated with toluene, then was dissolved in MeOH and reprecipitated with Et<sub>2</sub>O to afford the title compound (96.4 mg): MS (ES) m/e 421.9 (M+H)<sup>+</sup>.  
Anal. Calcd for C<sub>22</sub>H<sub>23</sub>N<sub>5</sub>O<sub>4</sub> · 0.25 H<sub>2</sub>O · TFA: C, 53.38; H, 4.57; N, 12.97. Found:  
15 C, 53.68; H, 4.97; N, 12.94.

### Example 59

Preparation of (±)-7-[[[(4,5-Dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid  
20

a) N-(Carbobenzyloxy)-N-(methyl)acetonitrile

Cbz chloride (7.40 mL, 49.3 mmol) was added slowly at RT to a solution of  
25 N methylaminoacetonitrile hydrochloride (5.0 g, 46.92 mmol) and triethylamine (13.4 mL, 96.2 mmol) in dichloromethane (200 mL). The reaction was stirred at RT 18 h, and the mixture was washed with 1N HCl, water and brine. The organic layer was dried (MgSO<sub>4</sub>) and concentrated to yield the title compound (6.97 g, 73%) as a clear oil.

30

b) N-(Carbobenzyloxy)-N-(methyl)aminothioacetamide

Hydrogen sulfide was bubbled through a solution of N-(carbobenzyloxy)-N-(methyl)acetonitrile (15 g, 73.5 mmol) and triethylamine (30.75 mL, 220.6 mmol) in DMF (250 mL). After 20 min, the flask was closed and the reaction was stirred at  
35 RT for 18 h. The reaction was then poured into 2 N NaHCO<sub>3</sub> (1 L) and extracted with dichloromethane. The combined organic phase was washed with 1:1

water/brine (5 x), dried ( $\text{MgSO}_4$ ), and concentrated to give a yellow oil which was purified by silica gel flash chromatography (step gradient, 40-50% ethyl acetate/hexane) to yield the title compound (12.26 g, 70%) as a white solid: MS (ES) m/e 239.0  $[\text{M}+\text{H}]^+$ .

5

c) N-(Carbobenzyloxy)-N-methyl-S-(methyl)acetothioimide

Iodomethane (17.66 mL, 283.6 mmol) was added at RT to a solution of N-(carbobenzyloxy)-N-(methyl)aminothioacetamide (6.75 g, 28.36 mmol) in acetone (100 mL). The solution was stirred at RT in the dark for 3 h, and the resulting precipitate was filtered to yield the title compound (9.63 g, 89%) as a white solid: MS (ES) m/e 253.4  $[\text{M}+\text{H}]^+$ .

10

d) ( $\pm$ )-2-Amino-3,3-dimethoxybutane

Sodium cyanoborohydride was added to a solution of 3,3-dimethoxy-2-butanone (1.32 g, 10 mmol) and ammonium acetate (1.1 g, 100 mmol) in methanol (30 mL). The pH was adjusted to 6 with methanolic HCl, and the reaction was stirred at RT overnight and concentrated. The residue was dissolved in water, and the pH was adjusted to 5 with aqueous HCl. The resulting solution was extracted with ether (3 x), and the aqueous phase was basified to pH 10 with  $\text{Na}_2\text{CO}_3$ , and extracted with ether. The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated to yield the title compound (1.1 g, 83%) as a clear oil: MS (ES) m/e 134.2  $[\text{M}+\text{H}]^+$ .

20

e) N-(Carbobenzyloxy)-N-methyl-(4,5-dimethyl-1H-imidazol-2-yl)methanamine

A solution of ( $\pm$ )-2-amino-3,3-dimethoxybutane (1.05 g, 7.89 mmol) and N-(carbobenzyloxy)-N-methyl-S-(methyl)acetothioimide (2.0 g, 5.26 mmol) in methanol (30 mL) was warmed at  $60^\circ\text{C}$  for 2 h, and concentrated to give a yellow oil. The crude oil was dissolved in 6 N HCl (30 mL) and stirred at RT 1 h. The solution was basified to pH 12 with aqueous NaOH and then extracted with dichloromethane. The combined organic phase was dried ( $\text{MgSO}_4$ ) and concentrated to give a brown oil which was purified by silica gel flash chromatography (4% methanol/dichloromethane) to yield the title compound (0.590 g, 41%) as a clear oil: MS (ES) m/e 274.0  $[\text{M}+\text{H}]^+$ .

30

f) N-Methyl-(4,5-dimethyl-1H-imidazol-2-yl)methanamine

A solution of N-(carbobenzyloxy)-N-methyl-(4,5-dimethyl-1H-imidazol-2-yl)methanamine (0.35 g, 1.28 mmol) in methanol (15 mL) and glacial acetic acid (5

35

mL), containing 10% Pd/C (0.035 g), was shaken in a H<sub>2</sub> atmosphere (45 Psi) for 6 h. The reaction was filtered and filtrate concentrated to give the title compound (0.22 g, 86%) as a brown oil which was used in the next step without further purification: MS (ES) m/e 140 [M+H]<sup>+</sup>.

5

g) Methyl (±)-7-[[[(4,5-dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

A solution of N-methyl-(4,5-dimethyl-1H-imidazol-2-yl)methanamine (0.20 g, 1.1 mmol) and methyl (±)-7-carboxy-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.320 g, 1.1 mmol) in the presence of DIEA (0.287 mL, 1.65 mmol) was stirred at RT. EDC (0.316 g, 1.65 mmol) was then added, followed by DMAP (0.013 g, 0.11 mmol). The mixture was stirred at RT for 18 h, and concentrated to give an oil which was purified by silica gel flash chromatography (step gradient, 0.5-2% methanol/dichloromethane) to yield the title compound (0.060 g, 9%) as a clear oil: MS (ES) m/e 414.2 [M+H]<sup>+</sup>.

15

h) (±)-7-[[[(4,5-Dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1 N Sodium hydroxide (3 eq) was added to a solution of methyl (±)-7-[[[(4,5-dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.060g, 0.145 mmol), the mixture was stirred at RT for 5 h, and concentrated. The residue was dissolved in water and the pH was adjusted to 5 with 50% acetic acid. The solution was concentrated and purified by MPLC (ODS-AQ, 10% acetonitrile/water containing 0.1% TFA, UV detection at 220 nm) to yield the title compound (0.050 g, 86%) as a white solid: MS (ES) m/e 400.2 [M+H]<sup>+</sup>.

25

#### Example 60

30 Preparation of 3-[[3-[2-(benzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoic acid

a) 4-(Benzimidazol-2-yl)-1-butene

According to the general procedures of Preparation 4 in P50256-1, except substituting 4-pentenoic acid for the Boc-sarcosine, the title compound is prepared.

35

b) 4-(1-Toluenesulfonylbenzimidazol-2-yl)-1-butene



Sodium hydride is added carefully to a solution of 4-(benzimidazol-2-yl)-1-butene (50 mmole) and 4-toluenesulfonyl chloride (55 mmole) in dry THF (200 mL). The reaction is stirred at RT until complete, then is quenched with saturated  $\text{NH}_4\text{Cl}$  (200 mL), and the mixture is extracted with EtOAc. The combined organic extracts are dried ( $\text{MgSO}_4$ ) and concentrated, and the residue is purified by silica gel chromatography to give the title compound.

c) 4-(1-Toluenesulfonylbenzimidazol-2-yl)-1-butanal

Ozone is bubbled into a solution of 4-(1-toluenesulfonylbenzimidazol-2-yl)-1-butene (40 mmole) in  $\text{CH}_2\text{Cl}_2$  (160 mL) and MeOH (40 mL) at  $-78^\circ\text{C}$  until the blue color persists, then the excess ozone is removed by bubbling argon through the solution. Dry dimethylsulfide (excess) is added, and the reaction is warmed to RT. The reaction is stirred at RT until complete, then is concentrated, and the residue is chromatographed on silica gel to afford the title compound.

d) 4-(1-Toluenesulfonylbenzimidazol-2-yl)-1-butanal oxime

Hydroxylamine hydrochloride (33 mmole) is added to a solution of 4-(1-toluenesulfonylbenzimidazol-2-yl)-1-butanal (30 mmole) and anhydrous sodium acetate (66 mmole) in MeOH (150 mL) at  $0^\circ\text{C}$ . The reaction is stirred at  $0^\circ\text{C}$  until complete, then is concentrated, and the residue is partitioned between  $\text{H}_2\text{O}$  and EtOAc. The layers are separated, and the aqueous layer is extracted with EtOAc. The combined organic layers are washed sequentially with 5%  $\text{NaHCO}_3$  and saturated brine, dried ( $\text{MgSO}_4$ ), and concentrated to afford the title compound.

e) 4-(1-Toluenesulfonylbenzimidazol-2-yl)-1-butanoximinoyl chloride

According to the procedure of Example 1(b) in WO 95/14682, except substituting 4-(1-toluenesulfonylbenzimidazol-2-yl)-1-butanal oxime for the 4-cyanobenzoxime, the title compound is prepared.

f) tert-Butyl [3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetate

According to the procedure of Example 1(d) of WO 95/14682, except substituting 4-(1-toluenesulfonylbenzimidazol-2-yl)-1-butanoximinoyl chloride for the 4-cyanobenzoximinoyl chloride, and substituting tert-butyl 3-butenate for the methyl 3-butenate, the title compound is prepared.

g) [3-[2-(1-Toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetic acid

4 M HCl in dioxane (10 mL) is added to a solution of tert-butyl [3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetate (5 mmole) in CH<sub>2</sub>CH<sub>2</sub> (40 mL) at 0°C. The reaction is stirred at RT until complete, then is concentrated to afford the title compound.

h) Ethyl 3-[[3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoate

EDC (1.2 mmole) is added to a solution of [3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetic acid (1 mmole), ethyl 3(R,S)-aminobutyrate (1.2 mmole), HOBT · H<sub>2</sub>O (1.2 mmole), and diisopropylethylamine (4 mmole) in anhydrous CH<sub>3</sub>CN (5 mL) at RT. The reaction is stirred at RT until complete, then is concentrated, and the residue is purified by silica gel chromatography to afford the title compound.

i) 3-[[3-[2-(Benzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoic acid

1.0 N LiOH (2.5 mmole) is added to a solution of ethyl 3-[[3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoate (0.5 mmole) in THF (2.5 mL). The reaction is stirred at RT until complete, then is neutralized with 1.0 N HCl. The solution is concentrated and the residue is purified by reverse-phase chromatography to afford the title compound.

#### Example 61

Preparation of 3-[3,4-dihydro-8-[[[(benzimidazol-2-yl)methyl][methylaminolcarbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoic acid

a) 2-Amino-4-iodobenzoic acid

The title compound is prepared from the oxidation of 4-iodo-2-nitrotoluene to give 4-iodo-2-nitrobenzoic acid according to the method of Sasson, et al., *J. Org. Chem.* **1986**, *51*, 2880-2883, followed by reduction of the nitro group using iron and acetic acid.

## b) 4-Iodoisatoic anhydride

To a mechanically stirred ice-cold solution of 2-amino-4-iodobenzoic acid (26.3 g, 0.1 mol), sodium carbonate (10.6 g, 0.1 mol) and water (250 mL), is slowly added, via an addition funnel, a solution of phosgene in toluene (80 mL of 1.93 M solution). After 2 h, the precipitated product is isolated by filtration and the solid is washed successively with water (200 mL), a 1:1 mixture of ethanol/ether (300 mL), and ether (200 mL). Drying under vacuum yields the title compound.

c) N-(2-Amino-4-iodobenzoyl)- $\beta$ -alanine benzyl ester

10 A magnetically stirred solution of 4-iodoisatoic anhydride (5.0 g, 0.0173 mol),  $\beta$  alanine benzyl ester tosylate (5.85 g, 0.0173 mol), and dimethylaminopyridine (0.5 g, 0.0041 mol) in pyridine (35 mL) is heated for 2 h at 80°C. The reaction mixture is allowed to cool to RT and concentrated in vacuo. The resulting residue is dissolved in ethyl acetate (100 mL), and washed  
15 successively with 10% cupric sulfate (2 x 50 mL), saturated sodium bicarbonate (1 x 50 mL) and brine (1 x 50 mL). Drying ( $\text{Na}_2\text{SO}_4$ ), filtration, concentration, and silica gel chromatography (1:1 EtOAc/hexanes) gives the title compound.

d) N-(4-Iodo-2-methylaminobenzoyl)- $\beta$ -alanine benzyl ester

20 A magnetically stirred solution of N-(2-amino-4-iodobenzoyl)- $\beta$ -alanine benzyl ester (2.0 mmol), 2,6-lutidine (0.35 mL, 3.0 mmol) and methyl iodide (0.19 mL, 3.0 mmol) in DMF (15 mL) is heated at 50°C for 15 h. The reaction mixture is allowed to cool to RT and concentrated in vacuo. The resulting residue is dissolved in ethyl acetate (75 mL), and washed successively with 10% citric acid (1 x 50 mL),  
25 saturated sodium bicarbonate (1 x 50 mL) and brine (1 x 50 mL). Drying ( $\text{Na}_2\text{SO}_4$ ), filtration, concentration, and silica gel chromatography (gradient 35-65 % EtOAc/hexanes) gives the title compound.

## e) Benzyl 3-[3,4-dihydro-8-iodo-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate

30 To a cold (-30°C) magnetically stirred solution of N-(4-iodo-2-methylaminobenzoyl)- $\beta$ -alanine benzyl ester (0.305 g, 0.69 mmol) and triethylamine (0.144 g, 1.04 mmol) in methylene chloride (3 mL) is added slowly a solution of  $\alpha$ -bromoacetyl bromide (0.09 mL, 1.04 mmol) in methylene chloride (2 mL) under  
35 argon. The reaction mixture is allowed to warm to RT and stir for 2 h. The mixture is diluted with methylene chloride (40 mL) and washed successively with 10% citric acid (1 x 50 mL) and saturated sodium bicarbonate (1 x 50 mL), dried ( $\text{Na}_2\text{SO}_4$ ),

filtered and concentrated in vacuo. The resulting residue is dissolved in DMF (3 mL) and added via an addition funnel to a slurry of sodium hydride (25 mg, 1.04 mmol) in DMF (2 mL) which is cooled to 0°C. After 2 h of stirring, the mixture is poured over an ice cooled solution of 10% citric acid (50 mL) and extracted with ethyl acetate (3 x 40 mL). The combined extracts are washed with saturated sodium bicarbonate (1 x 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Silica gel chromatography (gradient 40-70% EtOAc/hexanes) gives the title compound.

- 10 f) Benzyl-3-[3,4-dihydro-8-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate

A mixture of benzyl 3-[3,4-dihydro-8-iodo-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate (2 mmol), 2-(methylaminomethyl)benzimidazole dihydrochloride (3 mmol), DIEA (1.8 mL, 10 mmol), and (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (140 mg, 0.2 mmol) in N-methyl-2-pyrrolidinone (20 mL) is heated to 110°C under CO balloon for 3 h. The mixture is then concentrated and the residue is purified by silica gel flash chromatography to give the title compound.

- 20 g) 3-[3,4-Dihydro-8-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoic acid

A mixture of benzyl-3-[3,4-dihydro-8-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate (2 mmol) and 10% Pd/C (0.02 g) in ethanol (100 mL) is hydrogenated in an atmosphere of H<sub>2</sub> (50 psi) for 6 h. The catalyst is removed by filtration, and the filtrate is concentrated under vacuo to afford the title compound.

#### Example 62

- 30 Preparation of 3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]]-4-propanoic acid

- a) Ethyl N-(2-amino-4-iodobenzoyl)-β-alanine

A magnetically stirred solution of 4-iodoisatoic anhydride (0.0173 mol), β-alanine ethyl ester hydrochloride (0.0173 mol), and dimethylaminopyridine (0.5 g, 0.0041 mol) in pyridine (35 mL) is heated for 2 h at 80°C. The reaction mixture is allowed to cool to RT and concentrated in vacuo. The resulting residue is dissolved in ethyl acetate (100 mL), and washed successively with 10% cupric sulfate (2 x 50

mL), saturated sodium bicarbonate (1 x 50 mL) and brine (1 x 50 mL). Drying ( $\text{Na}_2\text{SO}_4$ ), filtration, concentration, and silica gel chromatography (1:1 EtOAc/hexanes) gives the title compound.

5 b) Ethyl-3-[3,4-dihydro-8-iodo-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate

To a cold ( $-30^\circ\text{C}$ ) magnetically stirred solution of ethyl N-(2-amino-4-iodobenzoyl)- $\beta$ -alanine (0.69 mmol), and triethylamine (0.144 g, 1.04 mmol) in methylene chloride (3 mL) is added slowly a solution of  $\alpha$ -bromoacetyl bromide (0.09 mL, 1.04 mmol) in methylene chloride (2 mL) under argon. The reaction mixture is allowed to warm to RT and stir for 2 h. The mixture is diluted with methylene chloride (40 mL) and wash successively with 10% citric acid (1 x 50 mL) and saturated sodium bicarbonate (1 x 50 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated in vacuo. The resulting residue is dissolved in DMF (3 mL) and added via an addition funnel to a slurry of sodium hydride (25 mg, 1.04 mmol) in DMF (2 mL) which is cooled to  $0^\circ\text{C}$ . After 2 h of stirring, the mixture is poured over an ice cooled solution of 10% citric acid (50 mL) and extracted with ethyl acetate (3 x 40 mL). The combined extracts are washed with saturated sodium bicarbonate (1 x 50 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, concentrated, and chromatographed on silica gel to afford the title compound.

20

c) Ethyl-3-[3,4-dihydro-8-iodo-2-thione-5-oxo-1H-1,4-benzodiazepine]-4-propanoate

To a solution of ethyl-3-[3,4-dihydro-8-iodo-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate (1.0 g, 2.49 mmol) in THF (10 mL) at RT and under an atmosphere of nitrogen is added Lawesson's reagent (1.0 g), and the reaction is heated at  $50^\circ\text{C}$  for 2 h. The reaction mixture is allowed to cool to RT and is concentrated in vacuo. Silica gel chromatography (gradient 40-60% EtOAc/hexanes) gives the title compound.

25

d) Ethyl-3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-iodo]-4-propanoate

To a vigorously stirred biphasic solution of ethyl-3-[3,4-dihydro-8-iodo-2-thione-5-oxo-1H-1,4-benzodiazepine]-4-propanoate (0.95 g, 2.27 mmol), methyl iodide (0.2 g) and a catalytic amount of tetrabutylammonium hydrogen sulfate in  $\text{CH}_2\text{Cl}_2$  (10 mL) and water (10 mL) is added 2 N NaOH (1.2 mL) at RT. After 2 h, the layers are separated and the aqueous layer is washed with  $\text{CH}_2\text{Cl}_2$  (2 x 25 mL). The combined organic extracts are dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The resulting residue is dissolved in toluene (10 mL) and treated with

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propargyl amine (0.64 mL, 4-fold excess) and pyridine hydrogen chloride (0.23 g, 1 mol eq). The reaction is heated to reflux for 6 h, then was allowed to cool to RT. Concentration and silica gel chromatography (EtOAc) gives the title compound.

5

e) Ethyl-3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]]-4-propanoate

A mixture of ethyl-3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-iodo]-4-propanoate (2 mmol), 2-(methylaminomethyl)benzimidazole (3 mmol), DIEA (1.8 mL, 10 mmol), and (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (140 mg, 0.2 mmol) in N-methyl-2-pyrrolidinone (20 mL) is heated to 110°C under a CO balloon for 3 h. The mixture is then concentrated and the residue is purified by silica gel flash chromatography to give the title compound.

15 f) 3-[4H-Imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]]-4-propanoic acid

A solution of ethyl-3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]]-4-propanoate (54 mmol), LiOH · H<sub>2</sub>O (0.79 mmol), THF (5 mL), and water (2 mL) is stirred at RT overnight. The mixture is concentrated, the residue is dissolved in water, and the resulting solution is neutralized with 3 N HCl. The precipitate is collected and dried in vacuo to afford the title compound.

25

#### Example 63

#### Preparation of 4-[4-[2-(1H-benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetic acid

30 a) Ethyl 4-[4-[(tert-butoxycarbonyl)]-1-piperazinyl]-1-piperidineacetate

The title compound is prepared from tert-butyl 1-piperazinecarboxylate (Aldrich) and ethyl 4-oxo-1-piperidineacetate (Porter et al. EPA 0 542 363 A2) by NaCNBH<sub>3</sub> reductive amination according to the method of Porter et al., EPA 0 542 363 A2.

35

b) Ethyl 4-(1-piperazinyl)-1-piperidineacetate

A solution of ethyl 4-[4-[(tert-butoxycarbonyl)]-1-piperazinyl]-1-piperidineacetate and 4 M HCl/dioxane in  $\text{CH}_2\text{Cl}_2$  is stirred at RT for 18 h. The reaction mixture is concentrated to give the title compound as the hydrochloride salt.

5 c) 2-[2-Chloroethyl]benzimidazole

A solution of 2-benzimidazoleethanol and thionyl chloride in  $\text{CH}_2\text{Cl}_2$  is heated at reflux for 2 h. The mixture is evaporated to give the title compound.

10 d) Ethyl of 4-[4-[2-(1H-benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetate

A solution of ethyl 4-(1-piperazinyl)-1-piperidineacetate, 2-[2-chloroethyl]benzimidazole, and DIEA in DMF is stirred at RT for 18 h. The mixture is concentrated and purified by chromatography to give the title compound.

15 e) 4-[4-[2-(1H-Benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetic acid

A solution of ethyl of 4-[4-[2-(1H-benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetate and 1.0 N NaOH in MeOH is stirred at RT. After 18 h, the mixture is neutralized with AcOH, desalted through an XAD-2 column, and lyophilized to give the title compound.

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Example 64

Preparation of 1-hydroxy-4-[4-[3-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexanecetic acid

25

a) tert-Butyl 1-hydroxy-4-[4-[2-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexaneacetate

A solution of tert-butyl 1-hydroxy-4-(1-piperazinyl)-cyclohexaneacetate (EPA 0 537 980 A1), 2-(3-bromopropyl)benzimidazole (*J. Org. Chem.* **1962**, *27*,  
30 2165), and DIEA in DMF is stirred at RT for 18 h. The mixture is concentrated and purified by chromatography to give the title compound.

b) 1-Hydroxy-4-[4-[2-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexaneacetic acid

35

A solution of tert-butyl 1-hydroxy-4-[4-[2-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexaneacetate and 4 M HCl/dioxane in  $\text{CH}_2\text{Cl}_2$  is stirred at RT. After 18 h, the mixture is evaporated to give the title compound.

Example 65Preparation of N-[3-[1-[[2-(2-Benzimidazolyl)ethyl]carbonyl]piperidinyl]carbonyl]-5  $\beta$ -alanine

Following the procedures of Beavers et. al., WO 95/25091, Example 1, except substituting (2-benzimidazolyl)propionic acid for N<sup>α</sup>-Boc-D-lys(Cbz)-OH, gives the title compound.

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Example 66Preparation of 2-[(Benzimidazol-2-yl)methyl]- 5-[2-(carboxy-ethyl)amino]carbonyl]-2,3-dihydro-3-oxo-1H-isoindole

15

Following the procedures of Preparation 1-12 in Hartman, et al., EP 0 540 334 A1, for the preparation of 1-H-isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxy-ethyl)-2-[2-(piperidinyl)ethyl]-3-oxo, except substituting 2-(aminomethyl)benzimidazole (Aldrich) for Boc-4-piperidine-2-ethylamine, the title compound is prepared.

20

Example 67Preparation of [3(R)-[2-(benzimidazol-2-yl)ethyl]-2-oxopiperidinyl]acetyl-3(R)-methyl - $\beta$ -alanine

25

## a) Methyl 4-(benzimidazol-2-yl) butanoate

Following the procedure of Example 36(a), except substituting 1,2-diaminobenzene for the 2,3-diaminopyridine, the title compound is prepared.

## 30 b) 4-(Benzimidazol-2-yl) butanoic acid

Following the procedure of Example 36(b), methyl 4-(benzimidazol-2-yl) butanoate is saponified to afford the title compound.

35 c) [3(R)-[2-(Benzimidazol-2-yl)ethyl]-2-oxopiperidinyl]acetyl-3(R)-methyl - $\beta$ -alanine



Following the procedure of Duggan et al (*J. Med. Chem.* 1995, 38, 3332), except using 4-(benzimidazol-2-yl) butanoic acid instead of (N-Boc-piperidin-4-yl)butanoic acid, the title compound is prepared.

5

Example 68Preparation of 4-[[[2-(benzimidazolyl)methyl]carbonyl]methylamino]-acetyl]phenoxyacetic acid a) 4-[2-(Boc-methylamino)acetyl]phenol

A solution of di-tert-butyl dicarbonate (5.96 g, 27.3 mmol) in 1,4-dioxane (25 mL) was added dropwise at 0°C to a mixture of 4-[2-(methylamino)acetyl]phenol hydrochloride (5.0 g, 24.8 mmol), 1,4-dioxane (30 mL), H<sub>2</sub>O (25 mL) and 1.0 N NaOH (25 mL, 25 mmol). After 24 h, the reaction was warmed to RT and stirred for 1.5 h. More 1.0 N NaOH (25 mL, 25 mmol) was added, and the reaction was stirred for an additional 0.5 h at RT, and concentrated. The residue was diluted with EtOAc (80 mL), and the mixture was acidified to pH 2 using 1.0 M NaHSO<sub>4</sub>. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed with H<sub>2</sub>O and dried (Na<sub>2</sub>SO<sub>4</sub>). Filtration and concentration gave the title compound (6.49 g, 99%): <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 6.70-8.05 (m, 4 H), 4.53 (s, 2H), 2.98 (s, 3H), 1.50 (s, 9H).

20

## b) Benzyl 4-[2-(Boc-methylamino)acetyl]phenoxyacetate

A mixture of the compound of Example 68(a) (5.04 g, 19.0 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.63 g, 19.0 mmol) in acetone (100 mL) was stirred at reflux under argon for 1h. The mixture was cooled to RT and benzyl bromoacetate (5.23 g, 22.8 mmol) was added. The reaction was heated at reflux for 18 h, then was cooled and filtered. The filter cake was washed with acetone, and the filtrate was concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) and washed sequentially with H<sub>2</sub>O (50 mL) and brine (50 mL). Drying (Na<sub>2</sub>SO<sub>4</sub>), concentration, and flash chromatography ( silica gel, 1:3 EtOAc/hexanes) yielded the title compound (7.28 g, 93%): <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 6.85-7.95 (m, 9 H), 5.23 (s, 2H), 4.71 (s, 2H), 4.55 (d, 2H), 2.95 (d, 3H), 1.45 (d, 9H).

30

## c) Benzyl 4-[2-(methylamino)acetyl]phenoxyacetate hydrochloride

A mixture of the compound of Example 68(b) (7.26 g, 17.57 mmol) and 4 M HCl in 1,4-dioxane (150 mL) was stirred for 1 h at RT. Concentration and trituration with Et<sub>2</sub>O afforded the title compound as a white powder (5.93 g, 97%):

35

<sup>1</sup>H NMR (250 MHz, CD<sub>3</sub>OD) δ 7.05-8.00 (m, 9 H), 5.23 (s, 2H), 4.88 (s, 2H), 4.65 (s, 2H), 2.80 (s, 3H).

d) Benzyl 4-[[[2-

5 (benzimidazolyl)methyl]carbonyl]methylamino]acetyl]phenoxyacetate

A mixture of the compound of Example 68(c) (1 mmol), 2-(benzimidazolyl)acetic acid (1 mmol), EDC (1.5 mmol), and DIEA (3 mmol) in DMF (25 mL) is stirred at RT. The mixture is poured in to 5% NaHCO<sub>3</sub> and extracted with EtOAc. The organic phase is washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue is chromatographed (silica gel) to give the title compound.

e) 4-[[[2-(Benzimidazolyl)methyl]carbonyl]methylamino]acetyl]phenoxyacetate

The compound of Example 68(d) (1 mmol) and 1N NaOH (1.5 mL) in CH<sub>3</sub>OH (20 mL) is stirred and concentrated. The residue is dissolved in H<sub>2</sub>O, extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous phase is adjusted to pH 5 with dilute HCl to give the title compound.

#### Example 69

20

Preparation of 4-[[[2-(Benzimidazolyl)methyl]carbonyl]methylamino]acetyl]-1,2-phenylenedioxydiacetic acid

a) 4-[2-(Boc-methylamino)acetyl]-1,2-dihydroxybenzene

25

Following the procedure of Example 68(a), except substituting adrenalone hydrochloride (5.0 g, 23.0 mmol) for 4-[2-(methylamino)acetyl]phenol hydrochloride, the title compound (1.2 g, 19%) was prepared following flash chromatography (silica gel, 1:1 EtOAc/hexanes): MS (ES) m/e 282.2 [M+H]<sup>+</sup>.

30 b) Dimethyl 4-[2-(Boc-methylamino)acetyl]-1,2-phenylenedioxydiacetate

Following the procedure of Example 68(b), except substituting the compound of Example 69(a) (0.9 g, 3.2 mmol) for the compound of Example 68(a) and methyl bromoacetate (1.23 g, 8.0 mmol) for benzyl bromoacetate, the title compound (1.11 g, 81%) was prepared: MS (ES) m/e 426.2 [M+H]<sup>+</sup>.

35

c) Dimethyl 4-[2-(methylamino)acetyl]-1,2-phenylenedioxydiacetate hydrochloride

Following the procedure of Example 68(c), except substituting the compound of Example 69(b) (1.11 g, 2.6 mmol) for the compound of Example 68(b), the title compound was prepared (1.1 g, quantitative): MS (ES) m/e 326.0 [M+H]<sup>+</sup>.

5

d) Dimethyl 4-[[[2-(benzimidazolyl)methyl]carbonyl]methylamino]acetyl]-1,2-phenylenedioxydiacetate

Following the procedure of procedure of Example 68(d), except substituting the compound of Example 69(c) for the compound of Example 68(c), gives the title compound.

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e) 4-[[[2-(Benzimidazolyl)methyl]carbonyl]methylamino]acetyl]-1,2-phenylenedioxydiacetic acid

Following the procedure of procedure of Example 68(e), except substituting the compound of Example 69(d) for the compound of Example 68(d), gives the title compound.

15

#### Example 70

20 Preparation of N-[3-[[[2-Benzimidazolyl)methyl]carbonyl]amino]benzoyl]-β-alanine

a) Benzyl N-[3-[[[2-benzimidazolyl)methyl]carbonyl]amino]benzoyl]-β-alaninate

A mixture of benzyl N-(3-aminobenzoyl)-β-alaninate (Alig, et. al., EPA 372486)(1 mmol), (2-benzimidazolyl)acetic acid (1 mmol), EDC (1.5 mmol), and DIEA (3 mmol) in DMF (25 mL) is stirred at RT. The mixture is poured into 5% NaHCO<sub>3</sub> and extracted with EtOAc. The combined organic phase is washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue is chromatographed (silica gel) to give the title compound.

30

b) N-[3-[[[2-Benzimidazolyl)methyl]carbonyl]amino]benzoyl]-β-alanine

A mixture of the compound of Example 70(a)(1 mmol) and 1N NaOH (1.5 mL) in CH<sub>3</sub>OH (20 mL) is stirred and concentrated. The residue is dissolved in H<sub>2</sub>O, extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous phase is adjusted to pH 5 with dilute HCl to give the title compound.

35

#### Example 71

Preparation of [[1-[N-[[[2-Benzimidazolyl)methyl]carbonyl]tyrosyl]-4-piperidinyl]oxy]acetic acid

- 5 a) tert-Butyl [[1-[N-[[[2-benzimidazolyl)methyl]carbonyl]tyrosyl]-4-piperidinyl]oxy]acetate

A mixture of tert-butyl [(1-tyrosyl-4-piperidinyl)oxy]acetate (Alig, et. al., EPA 372486)(1 mmol), (2-benzimidazolyl)acetic acid (1 mmol), EDC (1.5 mmol), and DIEA (3 mmol) in DMF (25 mL) is stirred at RT. The mixture is poured into  
 10 5% NaHCO<sub>3</sub> and extracted with EtOAc. The combined organic phase is washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue is chromatographed (silica gel) to give the title compound.

- b) [[1-[N-[[[2-Benzimidazolyl)methyl]carbonyl]tyrosyl]-4-piperidinyl]oxy]acetic  
 15 acid

A mixture of the compound of Example 71(a)(1 mmol) and CF<sub>3</sub>CO<sub>2</sub>H in CH<sub>2</sub>Cl<sub>2</sub> is stirred and concentrated to give the title compound.

Example 72

20

Preparation of (S)-4-[[[2-Benzimidazolyl)methyl]carbonyl]glycyl]-3-methoxycarbonylmethyl-2-oxopiperazine-1-acetic acid

Following the procedure of Sugihara, et. al., EP 0529858, Example 59, except substituting (2-benzimidazolyl)acetic acid for 4-amidinobenzoic acid  
 25 hydrochloride, gives the title compound.

Example 73

Preparation of (3S,5S)-5-[[4-[[2-Benzimidazolyl)methyl]phenyl]oxymethyl]-3-carboxymethyl-2-pyrrolidinone

30

- a) 4-[[2-Benzimidazolyl)methyl]phenol

Following the general procedure of Wahlgren and Addison, J. Heterocycl. Chem., 1989, 26, 541-543, except substituting 4-(hydroxy)phenylacetic acid for 2-  
 35 (hydroxy)phenylacetic acid, gives the title compound.

b) (3S,5S)-5-[[4-[(2-Benzimidazolyl)methyl]phenyl]oxymethyl]-3-[(tert-butoxycarbonyl)methyl]-2-pyrrolidinone

Following the procedure of Himmelsbach, et.al., Australian Patent Application AU-A-86926/91, Example 51, substituting the compound of Example 73(a) for 4'-cyano-3'-fluoro-4-hydroxy)biphenyl, gives the title compound.

c) (3S,5S)-5-[[4-[(2-Benzimidazolyl)methyl]phenyl]oxymethyl]-3-carboxymethyl-2-pyrrolidinone

The compound of Example 73(b) is treated with CF<sub>3</sub>CO<sub>2</sub>H in CH<sub>2</sub>Cl<sub>2</sub> to give the title compound.

#### Example 74

Preparation of 1-[(2-Benzimidazolyl)methyl]-3-[4-(2-carboxyethyl)phenyl]-4-methoxy-3-pyrrolin-2-one

Following the procedures of Linz, et. al., EP 0567968, except substituting (2-benzimidazolyl)methanamine for 4-cyanoaniline, gives the title compound.

#### Example 75

20

Preparation of 2-[6-(benzimidazol-2-yl) methylaminocarbonyl]-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

a) 6-Methoxy-1,2,3,4-tetrahydroisoquinoline

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6-Methoxy-1,2,3,4-tetrahydroisoquinoline is prepared according to the method of D. J. Sall and G. L. Grunewald (J. Med. Chem. 1987, 30, 2208-2216).

b) Ethyl 2-[6-Methoxy-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 75(a) (1.1 mmol), ethyl chloroacetate (1.17 mmol), and potassium carbonate (1.17 mmol) in acetonitrile (10 mL) is stirred for 18 hr. The mixture is then partitioned in a mixture of EtOAc and H<sub>2</sub>O. The organic phase is rotary evaporated to an oil, which is purified by silica gel chromatography to afford the title compound.

## c) Ethyl 2-[6-Hydroxy-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 75(b) (0.249 g, 1.0 mmol) and boron tribromide (1M in  $\text{CH}_2\text{Cl}_2$ , 1.0 mL, 1.0mmol, mL) is stirred at -70 °C for 2 hr and then stirred at RT for 12 hr. The solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed with water (1X), 5%  $\text{NaHCO}_3$  (2X), water (1X). EtOAc is dried over  $\text{Mg}_2\text{SO}_4$ , filtered and rotary evaporated to afford the title compound.

## d) Ethyl 2-[6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 75(c) (0.235 g, 1.0 mmol), trifluorosulfonic acid anyhdride (0.23 mL, 1.1mmol,) and  $\text{Et}_3\text{N}$  (0.32 mL, 1.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed with 5%  $\text{NaHCO}_3$  (2X), water (1X). EtOAc is dried over  $\text{Na}_2\text{SO}_4$ , filtered and rotary evaporated to afford the title compound.

## e) Ethyl 2-[6-carboxy-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 75(d) (0.367 g, 1.0mmol), palladium(II)bis-acetate (0.022 g, 0.1mmol,), triphenylphosphine (0.262 g, 1.0mmol), diisopropylamine (0.34 mL, 2.5 mmol), NMP (5 mL), in aqueous ammonium carbonate (10%) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

## f) Ethyl -[6-(benzimidazol-2-yl)methylaminocarbonyl]-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

A solution of the compound of Example 75(e) (0.263 g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.34g, 1.0 mmol), EDC (0.191g, 1.0 mmol), HOBt (0.151 g, 1.0 mmol) and triethylamine (0.235 mL, 2.0 mmol) in DMF(7 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel column to afford the title compound.

g) 2-[6-(benzimidazol-2-yl)methylaminocarbonyl]-1,2,3,4-tetrahydroisoquinoliny]acetic acid

A solution of the compound of Example 75(f) ( 0.42 g, 1.0 mmol) in aqueous  
5 1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol ( 5 mL) is stirred for 8 hr.  
The solution is rotary evaporated to an oil. The residue is purified by silica gel  
column to afford the title compound.

#### Example 76

10

Preparation of 2-[6-(benzimidazol-2-yl)methylaminocarbonyl]-1-oxo-1,2,3,4-tetrahydroisoquinoliny]acetic acid

a) 6-Methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline

15 6-Methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline is prepared according to the  
method of D. J. Sall and G. L. Grunewald, J. Med. Chem. (1987), 30, 2208-2216.

b) Ethyl 2-[6-Methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoliny]acetate

A mixture of the compound of Example 76(a) (0.39 mmol) and NaH (0.17 g,  
20 0.43 mmol, 60% oil dispersion) in THF (5 mL) is heated to reflux for 1 hr and then  
allowed to cool to room temperature. Ethyl chloroacetate (0.43 mmol) is added to  
the mixture, and the mixture is allowed to stir for 1 hr. The mixture is quenched  
with water (10 mL) and washed with EtOAc (2X 15 mL). The organic layers are  
combined, washed with water (10 mL) and rotary evaporated to an oil. The residue  
25 is purified by silica gel chromatography to afford the title compound.

c) Ethyl 2-[6-Hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoliny]acetate

A solution of the compound of Example 76(b) (0.263 g, 1.0 mmol) and  
boron tribromide (1M solution in CH<sub>2</sub>Cl<sub>2</sub>, 1.1 mL) is stirred at -70 °C for 2 hr and  
30 then at RT for 4 hr. The solution is rotary evaporated to an oil. The residue is taken  
up in EtOAc. EtOAc is washed with water (1X), 5% NaHCO<sub>3</sub> (2X), water (1X).

EtOAc is dried over  $\text{MgSO}_4$ , filtered and rotary evaporated to afford the title compound.

- d) Ethyl 2-[6-trifluoromethylsulfonyloxy-1-oxo-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 76(c) (3.4 mmol) and trifluorosulfonic acid anhydride (3.4 mmol, mL) in pyridine (5 mL) is chilled at 0° and allowed to warm to room temperature for 1 hr. The mixture is quenched with water (5 mL) and washed with EtOAc (2X 7 mL). The organic layers are combined, washed with water (7 mL) and rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

- e) Ethyl 2-[6-carboxy-1-oxo-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 76(d) (0.23 g, 1.0 mmol), palladium(II)bis-acetate (0.026 g, 0.1 mmol), triphenylphosphine (0.262 g, 1.0 mmol), diisopropylamine (0.23 mL, 2.0 mmol), NMP (7 mL), in aqueous ammonium carbonate "(10 %)" is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

- f) Ethyl -[6-(benzimidazol-2-yl)methylaminocarbonyl]-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

A solution of the compound of Example 76(e) (0.34 g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.43 g, 1.0 mmol), EDC (0.191 g, 1.0 mmol), HOBt (0.15 g, 1.0 mmol) and triethylamine (0.234 mL, 2.3 mmol) in DMF (8 mL) is stirred for 8 hr. The solution is concentrated. The residue is purified by silica gel chromatography to afford the title compound.

Alternatively, a solution of the compound of Example 76(d) (0.23 g, 1.0 mmol), palladium(II)bis-acetate (0.026 g, 0.1 mmol), triphenylphosphine (0.262 g, 1.0 mmol), diisopropylamine (0.25 mL, 2.1 mmol), NMP (7 mL), and the compound



of Intermediate A (0.31 g, 1.0 mmol) in aqueous ammonium carbonate (10%) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

5

g) 2-[6-((benzimidazol-2-yl)methylaminocarbonyl)-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

A The solution of the compound of Example 76(f) (0.25 g, 1.0 mmol) in aqueous 1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol (8 mL) is stirred for 8 hr. Solution is rotary evaporated to an oil. The residue is purified by silica gel to afford the title compound.

10

#### Example 77

15 Preparation of 2-[6-((benzimidazol-2-yl)methylcarbonylamino)tetralin]acetic acid

a) tert-butyl-5-amino-tetraline-2-acetate

Tert-butyl-5-amino-tetraline-2-acetate is prepared according to the methods described in M. J. Fisher, *et al.* (Scheme 12 and Example 28, parts A-D, EO 0635492, Jan. 25, 1995).

20

b) 2-[6-((benzimidazol-2-yl)methylcarbonylamino)tetralin]acetate

A solution of the compound of Example 77 (a) (0.261 g, 1.0 mmol), 2-(aminomethyl)benzimidazole (0.256g, 1.0 mmol), EDC (0.191g, 1.0 mmol) 1-hydroxybenzotriazole hydrate (0.152 g, 1.0 mmol), and triethylamine (0.234 mL, 2.1 mmol) in DMF (5 mL) is allowed to stir for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

25

30 A solution of the crude ester amide (0.32 g, 1.0 mmol) and trifluoroacetic acid (5 mL) in methylene chloride (5 mL) is allowed to stir for 1 hr. The solution is

rotary evaporated to an oil. The residue is treated with Et<sub>2</sub>O. Filtration and drying *in vacuo* afforded the title compound.

### Example 78

5

#### Preparation of 2-[6-((benzimidazol-2-yl)methylaminocarbonyl)tetralin]acetic acid

##### a) Ethyl-5-hydroxy-tetraline-2-acetate

The compound Ethyl-5-hydroxy-tetraline-2-acetic acid is prepared according  
10 to the method of M. J. Fisher *et al.* (EP 0635492, Scheme 6 and Example 20, parts A-D, p. 71).

##### b) Ethyl-5-trifluoromethylsulfonyloxy-tetraline-2-acetate

A solution of the compound of Example 78(b) (0.321g, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub>  
15 (10 mL) is cooled to 0° C. Trifluoromethylsulfonic acid anhydride (0.125 mL, 1.1 mmol) is added. The solution is stirred for 2 hr. The solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed with water (1X), 5% NaHCO<sub>3</sub>, water (1X). EtOAc is dried over MgSO<sub>4</sub>, filtered. Filtrate is rotary  
20 evaporated to afford the title compound.

##### c) Ethyl 6-carboxy-tetraline-2-acetate.

A solution of the compound of Example 78(c) (0.26 g, 1.0 mmol),  
palladium(II)bis-acetate (0.023g, 0.1 mmol), triphenylphosphine (0.262g, 1.0  
mmol), diisopropylamine (0.245 mL, 2.1 mmol), NMP (10 mL), in aqueous  
25 ammonium carbonate (10%) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

##### d) Ethyl -[6-((benzimidazol-2-yl)methylaminocarbonyl)-tetraline-1-acetate

30 A solution of the compound of Example 78(c) (0.34 g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.32g, 1.0 mmol), EDC (0.191 g, 1.0

mmol), HOBt (0.152 g, 1.0 mmol) and triethylamine (0.23 mL, 2.1 mmol) in DMF(6 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

5           Alternatively, a solution of the compound of Example 78(b) (0.34 g, 1.0 mmol), palladium(II)bis-acetate (0.023g, 0.1 mmol), triphenylphosphine (0.262g, 1.0 mmol), diisopropylamine (0.23 mL, 2.1 mmol), NMP (10 mL), and the compound of Intermediate A (0.32 g, 1.0 mmol), in aqueous ammonium carbonate (10%) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is  
10   rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

e) 2-[6-((benzimidazol-2-yl)methylaminocarbonyl)-tetraline-2-acetic acid.

          A solution of the compound of Example 78(d) (0.31 g, 1.0 mmol) in aqueous  
15   1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol ( 5 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

#### Example 79

20

Preparation of 2-[5-((benzimidazol-2-yl)methylcarbonylamino)-benzofuran]-propionic acid

a) Ethyl 1-carboxymethyloxy-4-nitrosalicylaldehyde

25           A solution of 1-hydroxy-4-nitrosalicylaldehyde (Aldrich) ( 0.167 g, 1.0 mmol), ethyl bromoacetate (0.166 g, 1.0mmol) potassium carbonate ( 0.276 g, 2.0mmol) and sodium iodide (0.015 g, 0.1 mmol) in THF ( 10mL) is heated to 80 °C for 24 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

30

b) Ethyl 2-carboxy-5-nitrobenzofuran

A solution of the compound of Example 79(a) (0.229 g, 1.0 mmol), DBU (0.152 g, 1.0 mmol) in ethyl alcohol ( 10 mL) is allowed to stir at RT for 18 hr. The solution is rotary evaporated to an oil and the residue is treated with EtOH (10 mL). The solution is bubbled with HCl.gas for 2 minutes and refluxed for 5 hr. The solution is rotary evaporated to an oil. EtOAc is added and washed with water (2X), 5% citric acid (2X), water (1X), 5% NaHCO<sub>3</sub> (2X) and water (1X). EtOAc is rotary evaporated to afford the title compound.

c) Ethyl 2-(2-carboxy)ethylene-5-nitrobenzofuran

10 A cold solution (-78 °C) of the compound of Example 79(b) ( 0.235 g, 1.0 mmol)in THF (5 mL) is treated with DiBAL ( 1.0 M in THF, 1.0 mL, 1.0 mmol). The solution is stirred at -78 °C for 30 minutes and RT for 3 hr. The solution is treated with CH<sub>3</sub>COOH (3 mL) followed by water (2 mL). The solution is rotary evaporated to an oil and treated with toluene to azeotrope off the acetic acid. Drying  
15 *in vacuo* afforded the crude aldehyde.

A solution of the phosphonate ester (0.224 g, 1.0 mmol),in THF (5 mL) is treated with sodium hydride (60% suspension in mineral oil, 0.04 g, 1.0 mmol)at 0° C for 1 hr. To the solution is added the aldehyde (0.235 g, 1.0 mmol). The solution  
20 is stirred at RT for 18 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

d) tert-butyl 2-[5-amino-benzofuranyl]propionate

A solution of the compound of Example 79(c) ( 0.261 g, 1.0 mmol) in  
25 ethanol ( 5 mL) containing 10% palladium-on-carbon(0.026 g, 10% wt) is hydrogenated at 45 psi for 1 hr. The solution is filtered through Celite and the filtrate is rotary evaporated to an oil. Silica gel chromatography affords the title compound.

30 e) 2-[5-((benzimidazol-2-yl)methylcarbonylamino)-benzofuran]-propionic acid

A solution of the compound of Example 79(d) ( 0.263 g, 1.0 mmol), EDC ( 0.191 g, 1.0 mmol), 1-hydroxybenzotriazole ( 0.150 g, 1.0 mmol), the compound of 2-(aminomethyl)benzimidazole ( 0.234 g, 1.0 mmol) and triethylamine (0.288 mL, 2.0 mmol) in DMF (5.0 mL) is allowed to stir for 18 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

A solution of the crude ester ( 0.263 g, 1.0 mmol) in MeOH (3.0 mL) is treated with 1 N NaOH (1.5 mL, 1.5 mmol) and water (2 mL). The solution is stirred at RT for 18 hr. The solution is rotary evaporated to an oil and purified by reversed phase chromatography to afford the title compound.

#### Example 80

##### 15 Preparation of 2-[5-((benzimidazol-2-yl)methylcarbonylamino)-2,3-dihydro-benzofuran]-propionic acid

##### a) Ethyl-2-[5-amino-2,3-dihydro-benzofuranyl]propionate

In the chromatographic purification of the compound of Example 79(d) the title compound is also obtained.

##### b) 2-[5-(6-aminopyridinyl-2-methylcarbonylamino)-benzofuran]-propionic acid

A solution of the compound of Example 80(a) (0.263 g, 1.0 mmol), EDC (0.191g, 1.0 mmol), 1-hydroxybenzotriazole (0.15g, 1.0 mmol), the compound of 2-(aminomethyl)benzimidazole (0.32 g, 1.0 mmol) and triethylamine (0.288 mL, 2.0 mmol) in DMF (5.0 mL) is allowed to stir for 18 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

A solution of the crude ester ( 0.290g, 1.0 mmol) in MeOH (5.0 mL) is treated with 1N NaOH (1.2 mL, 1.2 mmol) for 18 hr. The solution is rotary

evaporated to an oil and purified by reversed-phase chromatography to afford the title compound.

### Example 81

5

#### Preparation of 2-[5-(6-aminopyridinyl-2-methylaminocarbonyl)-benzofuran]-propionic acid

- a) 2-Ethoxycarbonyl-5-(tert-butyl-dimethylsilyloxy)-benzofuran
- 10 A solution of 2-Ethoxycarbonyl-5-(hydroxy)-benzofuran is prepared via the procedure described in M. L. Denny, *et al.* (EP 0655439, 31,5,95) (0.206 g, 1.0 mmol), tert-butyl-dimethylsilylchloride (0.23 mL, 1.0 mmol) and imidazole (0.34 g, 1.0 mmol) in THF is allowed to stir for 4 hr. The solution is rotary evaporated to an oil. EtOAc is added and washed with water. EtOAc is rotary evaporated to afford
- 15 the title compound.

b) 2-Hydrocarbonyl -5-(tert-butyl-dimethylsilyloxy)-benzofuran

- A cold solution (-78 °C) of the compound of Example 81(a) (0.35 g, 1.0 mmol) in THF (5 mL) is treated with DiBAL (1.0 M in THF, 1.0 mL, 1.0 mmol).
- 20 The solution is stirred at -78 °C for 30 minutes and RT for 3 hr. The solution is treated with CH<sub>3</sub>COOH (3 mL) followed by water (2 mL). The solution is rotary evaporated to an oil and treated with toluene to azeotrope off the acetic acid. Drying *in vacuo* afforded the aldehyde.

25 c) Ethyl 2-[5-(tert-butyl-dimethylsilyloxy)-benzofuran]-acrylate

- A solution of the phosphonate ester (0.224 g, 1.0 mmol), in THF (5 mL) is treated with sodium hydride (60% suspension in mineral oil, 0.04 g, 1.0 mmol) at 0° C for 1 hr. To the solution is added the above aldehyde (0.235 g, 1.0 mmol). The
- 30 solution is stirred at RT for 18 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

## d) 2-Ethyl 2-[-5-(hydroxy)-benzofuran]-propionate

A mixture of the compound of Example 81(c) (0.234g, 1.2 mmol) and 10% palladium-on-carbon (0.023 g, 10% wt) in EtOH( 5 mL).is hydrogenated at 50 psi for 1 hr. Filtration through Celite and concentration afforded.the ester (0.169 g, 56%).

A solution of the crude ester (0.34 g, 1.0 mmol) and tetraethylammonium fluoride (0.149 g, 1.0 mmol) in THF (10 mL) is allowed to stir at RT for 18 hr. The solution is rotary evaporated to an oil and purified by silica gel chromatography.

## e) 2-Ethyl 2-[-5-(trifluoromethylsulfonyloxy)-benzofuran]-propionate

A solution of the compound of Example 81(d) (0.366 g, 1.0 mmol) and Et<sub>3</sub>N(0.23 mL, 1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C is treated with trifluoromethylsulfonic acid anhydride (0.21 mL, 1.1 mmol). After 2 hr solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed successively with water(1X), 5% NaHCO<sub>3</sub> (2X), water (1X). EtOAc is dried over MgSO<sub>4</sub>, and filtered. Filtrate is rotary evaporated to afford the title compound.

## f) 2-Ethyl 2-[-5-(carboxy)-benzofuran]-propionate

A solution of the compound of Example 81(e) (0.366g, 1.0 mmol), palladium(II) bis-acetate (0.023g, 0.1 mmol), triphenylphospine (0.262g, 1.0 mmol), diisopropylethylamine (0.23 mL, 2.1 mmol), NMP (7 mL) in aqueous sodium bicarbonate (10%, 6 mL) is allowed to stir. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

## g) 2-Ethyl 2-[-5-(6-(6-aminopyridinyl)-2-methylaminocarbonyl)-benzofuran]-propionate

30

A solution of the compound of Example 81(f) (0.366 g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.23g, 1.0 mmol), EDC (0.191 g, 1.0mmol), HOBt (0.152g, 1.0mmol) and triethylamine (0.235 mL, 2.1mmol) in DMF(8 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

Alternatively, a solution of the compound of Example 81(e) (0.366g, 1.0mmol), palladium(II)bis-acetate (0.023g, 0.1 mmol), triphenylphosphine (0.262g, 1.0 mmol), diisopropylamine (0.23 mL, 2.1 mmol), NMP (10 mL ), and the compound of Intermediate A (0.32g, 1.0 mmol) in aqueous ammonium carbonate (10%, 10 mL) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

h) 2-[5-(6-(6-aminopyridinyl-2-methylaminocarbonyl)-benzofuran]-propionic acid  
A solution of the compound of Example 81(g) (0.366g, 1.0 mmol) in aqueous 1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol ( 8 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

#### Example 82

##### Preparation of 2-[5-((benzimidazol-2-yl)methylaminocarbonyl)-2,3-dihydro-benzofuran]-propionic acid

a) 2-tert-Butyl 2-[5-(hydroxy)-2,3-dihydro-benzofuran]-propionate

The chromatographic purification in Example 81(d) also provides the title compound.

b) 2-tert-Butyl 2-[5-(trifluoromethylsulfonyloxy)-2,3-dihydro-benzofuran]-propionate



A cold solution of the compound of Example 82(a) (0.28 g, 1.0 mmol) and Et<sub>3</sub>N (0.23 mL, 2.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) is treated with trifluoromethylsulfonic acid anhydride (0.15 mL, 1.1 mmol) for 2 hr. The solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed with water (1X), 5% NaHCO<sub>3</sub> (2X), water (1X). EtOAc is dried over MgSO<sub>4</sub>, filtered, and filtrate is rotary evaporated to afford the title compound.

c) 2-tert-Butyl 2-[-5-(carboxy)-2,3-dihydro-benzofuran]-propionate

A solution of the compound of Example 82(b) (0.24 g, 1.0 mmol), palladium(II) bis-acetate (0.023g, 0.1 mmol), triphenylphosphine (0.262g, 1.0 mmol), diisopropylethylamine (0.23 mL, 2.1 mmol), NMP (8 mL) in aqueous sodium bicarbonate (10 mL, 10%) is allowed to stir at RT for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

d) 2-tert-Butyl 2-[-5-(6-(6-aminopyridinyl-2-methylaminocarbonyl)-2,3-dihydro-benzofuran)-propionate

A solution of the compound of Example 82(c) (0.366g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.23g, 1.0 mmol), EDC (0.191g, 1.0 mmol), HOBt (0.152g, 1.0 mmol) and triethylamine (0.23 mL, 2.1 mmol) in DMF (8 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

Alternatively, a solution of the compound of Example 82(b) (0.366g, 1.0 mmol), palladium(II)bis-acetate (0.023 g, 0.1 mmol), triphenylphosphine (0.262 g, 1.0 mmol), diisopropylamine (0.23 mL, 2.1 mmol), NMP (10 mL), and the compound of Intermediate A (0.23 g, 1.0 mmol), in aqueous ammonium carbonate (10%, 10 mL) is stirred for 8 hr under an atmosphere of carbon monoxide for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

e) 2-[5-(6-((benzimidazol-2-yl)methylaminocarbonyl)-2,3-dihydro-benzofuran]-propionic acid

A solution of the compound of Example 82(d) (0.37 g, 1.0 mmol) in aqueous 1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol (8 mL) is stirred for 8 hr.

- 5 The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

### Example 83

10 Preparation of 1-[(1H-benzimidazol-2-yl)methyl]-3-[4[(2-ethoxycarbonyl)ethyl]phenyl]-3-oxo-imidazolidine

a) 2-Aminomethyl-1-p-toluenesulfonyl-benzimidazole

- 15 A solution of 2-Methylbenzimidazole (1 mmol), p-toluenesulfonyl chloride (1.05 mmol) and Et<sub>3</sub>N (1.05 mmol) in water (2 mL) and THF (1 mL) is allowed to stir for 4 hr. The mixture is concentrated by rotary evaporation and diluted with water (10 mL). The solution is washed with EtOAc (2X 15 mL). The organic layers are combined, washed with water (5 mL) and rotary evaporated to an oil.

- 20 A solution of the aforementioned oil (2-Methyl-1-p-toluenesulfonyl-benzimidazole) (1 mmol) and N-bromosuccinimide (1.05 mmol) in CCl<sub>4</sub> (10 mL) is allowed to reflux for 18 hr. Upon cooling a white solid precipitates from solution. The solid is filtered, triturated with CCl<sub>4</sub> and dried *in vacuo* to a solid.

- 25 A solution of Boc<sub>2</sub>NH (1 mmol) and potassium hydroxide (1 mmol) in ethanol (5 mL) is allowed to stir for 1 hr. Anhydrous ethyl ether (15 mL) is added and the mixture is filtered to afford the salt as a white solid. A solution of the aforementioned solid 2-bromomethyl-1-p-toluenesulfonylbenzimidazole (1 mmol) and (Boc)<sub>2</sub>N<sup>-</sup> K<sup>+</sup> (mmol) in THF (10 mL) is to stir at 60° for 18 hr. The mixture is
- 30 rotary evaporated to an oil.

- A solution of the 2-[bis-(tert-butyloxycarbonyl)aminomethyl]-1-p-toluenesulfonylbenzimidazole (1 mmol) in TFA (1.1 mmol) and CH<sub>2</sub>Cl<sub>2</sub> is allowed to stir for 1 hr. The solution is rotary evaporated to an oil, which is purified by
- 35 chromatography to afford the title compound.

## b) Ethyl 2-[4-(2-hydroxyethylamino)phenyl]propionate

This compound is prepared following the procedure of F. Himmelsbach *et al.* (Example V, p. 44, EP 0587134, Sept. 8, 1993), in which glycolaldehyde dimer (Aldrich) (mmol) is added to a solution of methyl 2-(4-aminophenyl)propionate 1 (1 mmol) in aqueous acetonitrile (pH 6-7) (mL), followed by sodiumcyanoborohydride (1.1 mmol), and the mixture is allowed to stir for 1 hr. The mixture is rotary evaporated to an oil, and the residue is dissolved in a mixture of ice water and ethyl acetate. The water layer is neutralized with 4 N sodium hydroxide and washed with ethyl acetate. The organic phase is rotary evaporated to an oil. A solution of the oil in ethyl acetate is purified on a silica gel column to give the title compound.

## c) N-[(1-p-toluenesulfonyl-1H-benzimidazol-2-yl)methyl]-N'-hydroxyethyl-N'-[4[(2-ethoxycarbonyl)ethyl]]phenyl]-urea

This compound is prepared following the procedures of F. Himmelsbach *et al.* (EP 0587134, Sept. 8, 1993 and EP 0612741, Feb.21, 1994), in which a solution of the compound of Example 83(a) (1 mmol) and phosgene (1.1 mmol) in THF (20 mL) is allowed to stir at -20° for 20 minutes. The compound of Example 83(b) (1.0 mmol) is added to the solution and the resulting mixture is allowed to stir for 18 hr. The resulting solution is rotary evaporated. A solution of the residue in ethyl acetate is washed with 5% citric acid, followed by water. The organic phase is rotary evaporated to an oil. A solution of the oil in ethyl acetate is purified on a silica gel column to give the title compound.

## d) N'-[(1-p-toluenesulfonyl-1H-benzimidazol-2-yl)methyl]-N'-[4[(2-ethoxycarbonyl)ethyl]]phenyl]-2-oxo-imidazolidine

This compound is prepared following the procedures of F. Himmelsbach *et al.* (Example III, EP 0587134, Sept. 8, 1993 and EP 0612741, Feb.21, 1994), in which a solution of the compound of Example 83(c) (1 mmol), methanesulfonylchloride (1.2 mmol) and triethylamine (1.2 mmol) in methylene chloride (5 mL) is allowed to stir at 0° for 1 hour. The mixture is partitioned in a mixture of water and methylene chloride. The organic phases are combined and dried over anhydrous sodium sulfate and rotary evaporated.

A solution of the residue and sodium iodide (1.1 mmol) in acetone (5 mL) is heated to reflux for 3 hr and then rotary evaporated to an oil. Potassium-bis(trimethylsilyl)azide (1.2 mmol) is added to a solution of the residue in DMF (5 mL), cooled to 0°. The solution is allowed to warm to room temperature over 30

min. and the rotary evaporated to an oil. The residue is partitioned in a mixture of water and methylene chloride. The organic phases are combined and dried over anhydrous sodium sulfate and rotary evaporated. A solution of the oil in ethyl acetate is purified on a silica gel column to give the title compound.

5

e) N<sup>1</sup>-[(1H-benzimidazol-2-yl)methyl]-N<sup>3</sup>-[4[(2-carboxyl)ethyl]phenyl]-2-oxoimidazolidine

A solution of the compound of Example 83(d) (1 mmol) in THF (5 mL) and 1 N sodium hydroxide (1.2 mL, 1.2 mmol) is allowed to stir for 18 hr. The mixture is neutralized with conc. hydrochloric acid and purified on a silica gel column to give the title compound.

10

#### Example 84

##### Parenteral Dosage Unit Composition

A preparation which contains 20 mg of the compound of Example 1 as a sterile dry powder is prepared as follows: 20 mg of the compound is dissolved in 15 mL of distilled water. The solution is filtered under sterile conditions into a 25 mL multi-dose ampoule and lyophilized. The powder is reconstituted by addition of 20 mL of 5% dextrose in water (D5W) for intravenous or intramuscular injection. The dosage is thereby determined by the injection volume. Subsequent dilution may be made by addition of a metered volume of this dosage unit to another volume of D5W for injection, or a metered dose may be added to another mechanism for dispensing the drug, as in a bottle or bag for IV drip infusion or other injection-infusion system.

25

#### Example 85

##### Oral Dosage Unit Composition

A capsule for oral administration is prepared by mixing and milling 50 mg of the compound of Example 1 with 75 mg of lactose and 5 mg of magnesium stearate. The resulting powder is screened and filled into a hard gelatin capsule.

30

#### Example 86

##### Oral Dosage Unit Composition

A tablet for oral administration is prepared by mixing and granulating 20 mg of sucrose, 150 mg of calcium sulfate dihydrate and 50 mg of the compound of

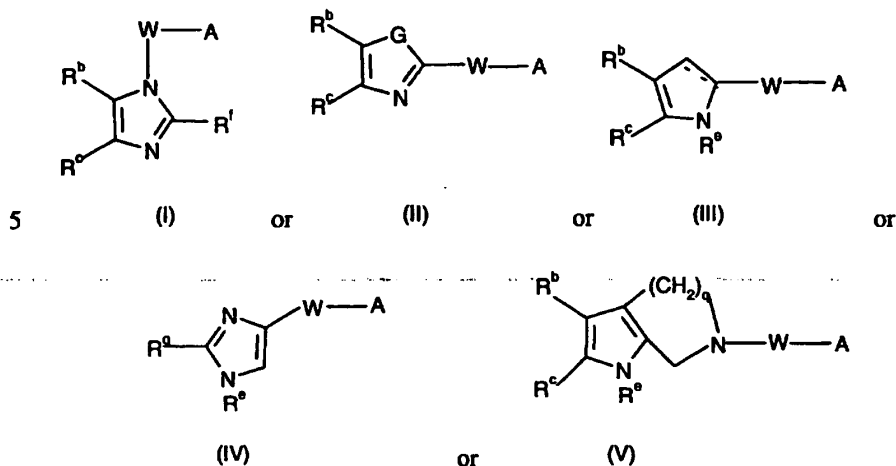
35

Example 1 with a 10% gelatin solution. The wet granules are screened, dried, mixed with 10 mg starch, 5 mg talc and 3 mg stearic acid; and compressed into a tablet.

5           The above description fully discloses how to make and use the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprises the state of the art and are  
10   incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound according to formula (I) or (II) or (III) or (IV) or (V):



wherein:

W is - (CHR<sup>g</sup>)<sub>b</sub>-V'- or phenyl;

10 A is a fibrinogen receptor antagonist template;  
V' is CONR<sup>21</sup> or NR<sup>21</sup>CO;

G is NR<sup>e</sup>, S or O;

R<sup>g</sup> is H, C<sub>1-6</sub>alkyl, Het-C<sub>0-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl or Ar-C<sub>0-6</sub>alkyl;

R<sup>21</sup> is Het-(CH<sub>2</sub>)<sub>0-6</sub>-U'-(CH<sub>2</sub>)<sub>1-6</sub>-, C<sub>3-7</sub>cycloalkyl-(CH<sub>2</sub>)<sub>0-6</sub>-U'-(CH<sub>2</sub>)<sub>1-6</sub>-, or

15 Ar-(CH<sub>2</sub>)<sub>0-6</sub>-U'-(CH<sub>2</sub>)<sub>1-6</sub>-;

U' is CONR<sup>f</sup> or NR<sup>f</sup>CO;

R<sup>f</sup> is H, C<sub>1-6</sub>alkyl or Ar-C<sub>1-6</sub>alkyl;

R<sup>e</sup> is H, C<sub>1-6</sub>alkyl, Ar-C<sub>1-6</sub>alkyl, Het-C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>1-6</sub>alkyl,

(CH<sub>2</sub>)<sub>q</sub>OH or (CH<sub>2</sub>)<sub>k</sub>CO<sub>2</sub>R<sup>g</sup>;

20 k is 0, 1 or 2;

q is 1 or 2;

b is 0, 1 or 2;

R<sup>b</sup> and R<sup>c</sup> are independently selected from H, C<sub>1-6</sub>alkyl, Ar-C<sub>0-6</sub>alkyl, Het-

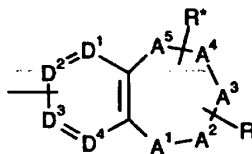
C<sub>0-6</sub>alkyl, or C<sub>3-6</sub>cycloalkyl-C<sub>0-6</sub>alkyl, halogen, CF<sub>3</sub>, OR<sup>f</sup>, S(O)<sub>k</sub>R<sup>f</sup>, COR<sup>f</sup>,

25 NO<sub>2</sub>, N(R<sup>f</sup>)<sub>2</sub>, CO(NR<sup>f</sup>)<sub>2</sub>, CH<sub>2</sub>N(R<sup>f</sup>)<sub>2</sub>, or R<sup>b</sup> and R<sup>c</sup> are joined together to

form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen,  $\text{CF}_3$ ,  $\text{C}_{1-4}\text{alkyl}$ ,  $\text{OR}^f$ ,  $\text{S(O)}_k\text{R}^f$ ,  $\text{COR}^f$ ,  $\text{CO}_2\text{R}^f$ ,  $\text{OH}$ ,  $\text{NO}_2$ ,  $\text{N(R}^f)_2$ ,  $\text{CO(NR}^f)_2$ , and  $\text{CH}_2\text{N(R}^f)_2$ , or methylenedioxy;

5 or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the fibrinogen receptor antagonist template A is



10 wherein:

$\text{A}^1$  to  $\text{A}^5$  form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from the group of O, S and N wherein S and N may be optionally oxidized;

15  $\text{D}^1$  to  $\text{D}^4$  form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

R is at least one substituent chosen from the group of  $\text{R}^7$ , or  $\text{Q-C}_{1-4}\text{alkyl}$ ,  $\text{Q-C}_{2-4}\text{alkenyl}$ ,  $\text{Q-C}_{2-4}\text{alkynyl}$ , optionally substituted by one or more of  $=\text{O}$ ,  $\text{R}^{11}$  or  $\text{R}^7$ ;

20  $\text{R}^*$  is H,  $\text{Q-C}_{1-6}\text{alkyl}$ ,  $\text{Q-C}_{1-6}\text{oxoalkyl}$ ,  $\text{Q-C}_{2-6}\text{alkenyl}$ ,  $\text{Q-C}_{3-4}\text{oxoalkenyl}$ ,  $\text{Q-C}_{3-4}\text{oxoalkynyl}$ ,  $\text{Q-C}_{2-4}\text{alkynyl}$ ,  $\text{C}_{3-6}\text{cycloalkyl}$ , Ar or Het, optionally substituted by one or more of  $\text{R}^{11}$ ;

Q is H,  $\text{C}_{3-6}\text{cycloalkyl}$ , Het or Ar;

$\text{R}^7$  is  $-\text{COR}^8$ ,  $-\text{COCR}'_2\text{R}^9$ ,  $-\text{C(S)R}^8$ ,  $-\text{S(O)}_m\text{OR}'$ ,  $-\text{S(O)}_m\text{NR}'\text{R}''$ ,  $-\text{PO(OR)'}$ ,  $-\text{PO(OR')}_2$ ,  $-\text{B(OR')}_2$ ,  $-\text{NO}_2$  and Tet;

25  $\text{R}^8$  is  $-\text{OR}'$ ,  $-\text{NR}'\text{R}''$ ,  $-\text{NR}'\text{SO}_2\text{R}'$ ,  $-\text{NR}'\text{OR}'$ ,  $-\text{OCR}'_2\text{C(O)OR}'$ ,  $-\text{OCR}'_2\text{OC(O)-R}'$ ,  $-\text{OCR}'_2\text{C(O)NR}'_2$ ,  $\text{CF}_3$  or AA;

$\text{R}^9$  is  $-\text{OR}'$ ,  $-\text{CN}$ ,  $-\text{S(O)}_r\text{R}'$ ,  $\text{S(O)}_m\text{NR}'_2$ ,  $-\text{C(O)R}'\text{C(O)NR}'_2$  or  $-\text{CO}_2\text{R}'$ ;

30  $\text{R}^{11}$  is H, halo,  $-\text{OR}^{12}$ ,  $-\text{CN}$ ,  $-\text{NR}'\text{R}^{12}$ ,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $\text{CF}_3\text{S(O)}_r$ ,  $-\text{CO}_2\text{R}'$ ,  $-\text{CONR}'_2$ ,  $\text{Q-C}_{0-6}\text{alkyl}$ ,  $\text{Q-C}_{1-6}\text{oxoalkyl}$ ,  $\text{Q-C}_{2-6}\text{alkenyl}$ ,  $\text{Q-C}_{2-6}\text{alkynyl}$ ,  $\text{Q-C}_{0-6}\text{alkyloxy}$ ,  $\text{Q-C}_{0-6}\text{alkylamino}$  or  $\text{Q-C}_{0-6}\text{alkyl-S(O)}_r$ ;

$\text{R}^{12}$  is  $\text{R}'$ ,  $-\text{C(O)R}'$ ,  $-\text{C(O)NR}'_2$ ,  $-\text{C(O)OR}^{15}$ ,  $-\text{S(O)}_m\text{R}'$  or  $\text{S(O)}_m\text{NR}'_2$ ;

$\text{R}^{13}$  is  $\text{R}'$ ,  $-\text{CF}_3$ ,  $-\text{SR}'$ , or  $-\text{OR}'$ ;

$\text{R}^{14}$  is  $\text{R}'$ ,  $\text{C(O)R}'$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $\text{SO}_2\text{R}'$  or  $\text{C(O)OR}^{15}$ ;

R<sup>15</sup> is H, C<sub>1-6</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;

R' is H, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-4</sub>alkyl or Ar-C<sub>0-4</sub>alkyl;

R" is R', -C(O)R' or -C(O)OR<sup>15</sup>;

R''' is R" or AA2;

- 5 AA1 is an amino acid attached through its amino group and having its carboxyl group optionally protected, and AA2 is an amino acid attached through its carboxyl group, and having its amino group optionally protected;

m is 1 or 2;

n is 0 to 3;

- 10 p is 0 or 1; and

t is 0 to 2; or

pharmaceutically acceptable salts thereof.

3. A compound according to claim 2 wherein:

- 15 A<sup>1</sup> is CR<sup>1</sup>R<sup>1'</sup>, CR<sup>1</sup>, NR<sup>1</sup>, N, O or S(O)<sub>x</sub>;

A<sup>2</sup> is CR<sup>2</sup>R<sup>2'</sup>, CR<sup>2</sup>, NR<sup>2</sup>;

A<sup>3</sup> is CR<sup>3</sup>R<sup>3'</sup>, CR<sup>3</sup>, NR<sup>3</sup>, N, O or S(O)<sub>x</sub>;

A<sup>4</sup> is CR<sup>4</sup>R<sup>4'</sup>, CR<sup>4</sup>, NR<sup>4</sup>, or N;

A<sup>5</sup> is CR<sup>5</sup>R<sup>5'</sup>, CR<sup>5</sup>, NR<sup>5</sup>, N, O or S(O)<sub>x</sub>;

- 20 D<sup>1</sup>-D<sup>4</sup> are CH or N;

R<sup>1</sup> and R<sup>1'</sup> are R\* or R, or together are =O;

R<sup>2</sup> and R<sup>2'</sup> are R\*, R or =O;

R<sup>3</sup> and R<sup>3'</sup> are R\*, R or =O;

R<sup>4</sup> and R<sup>4'</sup> are R\*, R or =O;

- 25 R<sup>5</sup> and R<sup>5'</sup> are R\*, R or =O; and

x is 0, 1 or 2.

4. A compound according to claim 2 wherein:

- 30 A<sup>1</sup> is CR<sup>1</sup>R<sup>1'</sup>, CR<sup>1</sup>, NR<sup>1</sup>, N, O or S; A<sup>2</sup> is CR<sup>2</sup>R<sup>2'</sup>, NR<sup>2</sup> or CR<sup>2</sup>; A<sup>3</sup> is CR<sup>3</sup>R<sup>3'</sup>; A<sup>4</sup> is CR<sup>4</sup>R<sup>4'</sup>, CR<sup>4</sup>, NR<sup>4</sup>, or N; A<sup>5</sup> is CR<sup>5</sup>R<sup>5'</sup>, CR<sup>5</sup>, NR<sup>5</sup>, N, O; D<sup>1</sup> and D<sup>4</sup> are CH; D<sup>2</sup> or D<sup>3</sup> is CH<sub>6</sub>; R<sup>2</sup> or R<sup>4</sup> are R; R<sup>3</sup>, R<sup>3'</sup> and R<sup>5</sup>, R<sup>5'</sup> are =O or R\*, H.

5. A compound according to claim 2 wherein:

- 35 A<sup>1</sup> is CHR<sup>1</sup>, CR<sup>1</sup>, NR<sup>1</sup>, N or S; A<sup>2</sup> is CR<sup>2</sup> or CR<sup>2</sup>R<sup>2'</sup>; A<sup>3</sup> is CR<sup>3</sup>R<sup>3'</sup>; A<sup>4</sup> is CR<sup>4</sup>R<sup>4'</sup> or NR<sup>4</sup>; A<sup>5</sup> is CR<sup>5</sup>R<sup>5'</sup> D<sup>1</sup>- D<sup>4</sup> are CH.

6. A compound according to claim 2 wherein:



$A^1$  is  $CR^1$ ,  $A^2$  is  $CR^2$ ,  $A^3$  is  $C=O$ ,  $A^4$  is  $NR^4$  and  $A^5$  are  $CHR^5$ .

7. A compound according to claim 2 wherein:

$A^1$  is  $NR^1$ ,  $A^2$  is  $CHCR^2$ ,  $A^3$  is  $CR^3R^{3'}$ ,  $A^4$  is  $NR^4$ , and  $A^5$  are  $C=O$ .

5

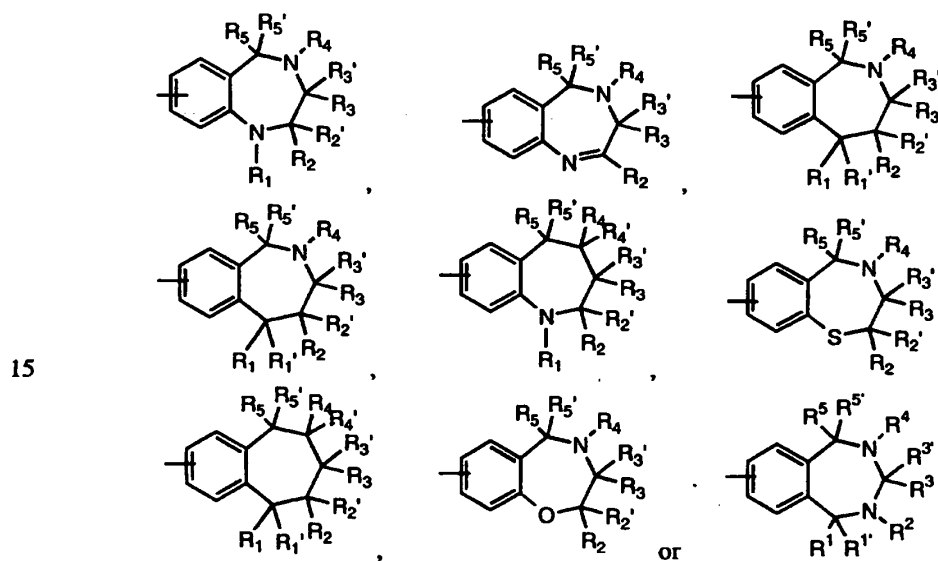
8. A compound according to claim 2 wherein:

$A^1$  and  $A^4$  are  $C=O$ ,  $A^2$  is  $NR^2$ ,  $A^3$  is  $CHR^{3'}$  and  $A^5$  is  $NR^5$ .

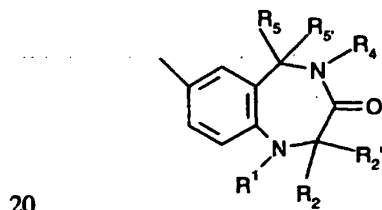
9. A compound according to claim 2 wherein:

10  $A^1$  is  $NR^1$ ,  $A^2$  is  $CHR^2$ ,  $A^3$  is  $C=O$ ,  $A^4$  is  $NR^4$  and  $A^5$  is  $CHR^5$ .

10. A compound according to claim 2 wherein:



11. A compound according to claim 2 wherein:

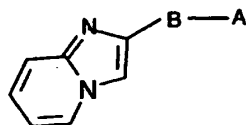


12. A compound according to claim 11 wherein:

$R^1$  is H or  $C_{1-4}$ alkyl;  $R^2, R^{2'}$  are H,  $-CH_2CO_2H$ ; and  $R^5R^{5'}$  are H, H.

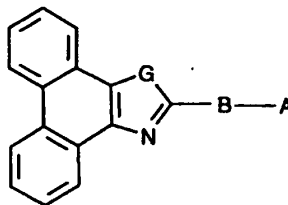
13. A compound according to formula (XXI) or (XXII):

5



(XXI)

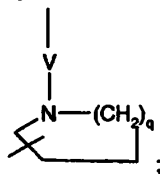
or



(XXII)

wherein:

B is  $-(CHR^g)_a-U-$   $(CHR^g)_b-V-$  or phenyl or



10 A is a fibrinogen receptor antagonist template;

U and V are absent or CO,  $CR^g_2$ ,  $C(=CR^g_2)$ ,  $S(O)_k$ , O,  $NR^g$ ,  $CR^gOR^g$ ,

$CR^g(OR^k)CR^g_2$ ,  $CR^g_2CR^g(OR^k)$ ,  $C(O)CR^g_2$ ,  $CR^g_2C(O)$ ,  $CONR^iNR^iCO$

$OC(O)$ ,  $C(O)O$ ,  $C(S)O$ ,  $OC(S)$ ,  $C(S)NR^g$ ,  $NR^gC(S)$ ,  $S(O)_2NR^g$ ,  $NR^gS(O)_2$

$N=N$ ,  $NR^gNR^g$ ,  $NR^gCR^g_2$ ,  $NR^gCR^g_2$ ,  $CR^g_2O$ ,  $OCR^g_2$ ,  $C\equiv C$  or  $CR^g=CR^g$ ;

15 G is  $NR^e$ , S or O;

$R^g$  is H,  $C_{1-6}$ alkyl, Het- $C_{0-6}$ alkyl,  $C_{3-7}$ cycloalkyl- $C_{0-6}$ alkyl or Ar- $C_{0-6}$ alkyl;

$R^k$  is  $R^g$ ,  $-C(O)R^g$ , or  $-C(O)OR^f$ ;

$R^i$  is H,  $C_{1-6}$ alkyl, Het- $C_{0-6}$ alkyl,  $C_{3-7}$ cycloalkyl- $C_{0-6}$ alkyl, Ar- $C_{0-6}$ alkyl,

Het- $(CH_2)_{0-6}-U'-(CH_2)_{1-6}-$ ,  $C_{3-7}$ cycloalkyl- $(CH_2)_{0-6}-U'-(CH_2)_{1-6}-$ , or

20 Ar- $(CH_2)_{0-6}-U'-(CH_2)_{1-6}-$  or  $C_{1-6}$ alkyl substituted by one to three groups

chosen from halogen, CN,  $NR^g_2$ ,  $OR^g$ ,  $SR^g$ ,  $CO_2R^g$ , and  $CON(R^g)_2$ ;

$R^f$  is H,  $C_{1-6}$ alkyl or Ar- $C_{1-6}$ alkyl;

$R^e$  is H,  $C_{1-6}$ alkyl, Ar- $C_{1-6}$ alkyl, Het- $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl- $C_{1-6}$ alkyl,

$(CH_2)_qOH$  or  $(CH_2)_kCO_2R^g$ ;

U' is CONR<sup>f</sup> or NR<sup>f</sup>CO;

k is 0, 1 or 2;

q is 1 or 2;

a is 0, 1 or 2;

5 b is 0, 1 or 2;

R<sup>b</sup> and R<sup>c</sup> are independently selected from H, C<sub>1-6</sub>alkyl, Ar-C<sub>0-6</sub>alkyl, Het-

C<sub>0-6</sub>alkyl, or C<sub>3-6</sub>cycloalkyl-C<sub>0-6</sub>alkyl, halogen, CF<sub>3</sub>, OR<sup>f</sup>, S(O)<sub>k</sub>R<sup>f</sup>, COR<sup>f</sup>,

NO<sub>2</sub>, N(R<sup>f</sup>)<sub>2</sub>, CO(NR<sup>f</sup>)<sub>2</sub>, CH<sub>2</sub>N(R<sup>f</sup>)<sub>2</sub>, or R<sup>b</sup> and R<sup>c</sup> are joined together to

form a five or six membered aromatic or non-aromatic carbocyclic or

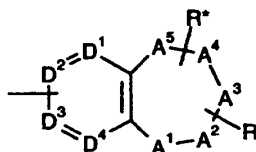
10 heterocyclic ring, optionally substituted by up to three substituents chosen

from halogen, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, OR<sup>f</sup>, S(O)<sub>k</sub>R<sup>f</sup>, COR<sup>f</sup>, CO<sub>2</sub>R<sup>f</sup> OH, NO<sub>2</sub>,

N(R<sup>f</sup>)<sub>2</sub>, CO(NR<sup>f</sup>)<sub>2</sub>, and CH<sub>2</sub>N(R<sup>f</sup>)<sub>2</sub>; or methylenedioxy;

or pharmaceutically acceptable salts thereof.

15 14. A compound according to claim 13 wherein the fibrinogen receptor antagonist template A is



wherein:

20 A<sup>1</sup> to A<sup>5</sup> form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from the group of O, S and N wherein S and N may be optionally oxidized;

D<sup>1</sup> to D<sup>4</sup> form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

25 R is at least one substituent chosen from the group of R<sup>7</sup>, or Q-C<sub>1-4</sub>alkyl, Q-C<sub>2-4</sub>alkenyl, Q-C<sub>2-4</sub>alkynyl, optionally substituted by one or more of =O, R<sup>11</sup> or R<sup>7</sup>;

R\* is H, Q-C<sub>1-6</sub>alkyl, Q-C<sub>1-6</sub>oxoalkyl, Q-C<sub>2-6</sub>alkenyl, Q-C<sub>3-4</sub>oxoalkenyl, Q-C<sub>3-4</sub>oxoalkynyl, Q-C<sub>2-4</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, Ar or Het, optionally substituted by one or more of R<sup>11</sup>;

30 Q is H, C<sub>3-6</sub>cycloalkyl, Het or Ar;

R<sup>7</sup> is -COR<sup>8</sup>, -COCR'<sub>2</sub>R<sup>9</sup>, -C(S)R<sup>8</sup>, -S(O)<sub>m</sub>OR', -S(O)<sub>m</sub>NR'R'', -PO(OR'), -PO(OR')<sub>2</sub>, -B(OR')<sub>2</sub>, -NO<sub>2</sub> and Tet;

- $R^8$  is  $-OR'$ ,  $-NR''$ ,  $-NR'SO_2R'$ ,  $-NR'OR'$ ,  $-OCR'_2C(O)OR'$ ,  $-OCR'_2OC(O)-$   
 $R'$ ,  $-OCR'_2C(O)NR'_2$ ,  $CF_3$  or  $AA$ ;  
 $R^9$  is  $-OR'$ ,  $-CN$ ,  $-S(O)_rR'$ ,  $S(O)_mNR'_2$ ,  $-C(O)R' C(O)NR'_2$  or  $-CO_2R'$ ;  
 $R^{11}$  is  $H$ ,  $halo$ ,  $-OR^{12}$ ,  $-CN$ ,  $-NR'R^{12}$ ,  $-NO_2$ ,  $-CF_3$ ,  $CF_3S(O)_r$ ,  $-CO_2R'$ ,  
5  $-CONR'_2$ ,  $Q-C_{0-6}alkyl$ ,  $Q-C_{1-6}oxoalkyl$ ,  $Q-C_{2-6}alkenyl$ ,  $Q-C_{2-6}alkynyl$ ,  $Q-C_{0-6}alkyloxy$ ,  $Q-C_{0-6}alkylamino$  or  $Q-C_{0-6}alkyl-S(O)_r$ ;  
 $R^{12}$  is  $R'$ ,  $-C(O)R'$ ,  $-C(O)NR'_2$ ,  $-C(O)OR^{15}$ ,  $-S(O)_mR'$  or  $S(O)_mNR'_2$ ;  
 $R^{13}$  is  $R'$ ,  $-CF_3$ ,  $-SR'$ , or  $-OR'$ ;  
 $R^{14}$  is  $R'$ ,  $C(O)R'$ ,  $CN$ ,  $NO_2$ ,  $SO_2R'$  or  $C(O)OR^{15}$ ;  
10  $R^{15}$  is  $H$ ,  $C_{1-6}alkyl$  or  $Ar-C_{0-4}alkyl$ ;  
 $R'$  is  $H$ ,  $C_{1-6}alkyl$ ,  $C_{3-7}cycloalkyl-C_{0-4}alkyl$  or  $Ar-C_{0-4}alkyl$ ;  
 $R''$  is  $R'$ ,  $-C(O)R'$  or  $-C(O)OR^{15}$ ;  
 $R'''$  is  $R''$  or  $AA_2$ ;  
 $AA_1$  is an amino acid attached through its amino group and having its  
15 carboxyl group optionally protected, and  $AA_2$  is an amino acid attached through its  
carboxyl group, and having its amino group optionally protected;  
 $m$  is 1 or 2;  
 $n$  is 0 to 3;  
 $p$  is 0 or 1; and  
20  $t$  is 0 to 2; or  
pharmaceutically acceptable salts thereof.

15. A compound according to claim 14 wherein:  
 $A^1$  is  $CR^1R^1$ ,  $CR^1$ ,  $NR^1$ ,  $N$ ,  $O$  or  $S(O)_x$ ;  
25  $A^2$  is  $CR^2R^2$ ,  $CR^2$ ,  $NR^2$ ;  
 $A^3$  is  $CR^3R^3$ ,  $CR^3$ ,  $NR^3$ ,  $N$ ,  $O$  or  $S(O)_x$ ;  
 $A^4$  is  $CR^4R^4$ ,  $CR^4$ ,  $NR^4$ , or  $N$ ;  
 $A^5$  is  $CR^5R^5$ ,  $CR^5$ ,  $NR^5$ ,  $N$ ,  $O$  or  $S(O)_x$ ;  
 $D^1-D^4$  are  $CH$  or  $N$ ;  
30  $R^1$  and  $R^{1'}$  are  $R^*$  or  $R$ , or together are  $=O$ ;  
 $R^2$  and  $R^{2'}$  are  $R^*$ ,  $R$  or  $=O$ ;  
 $R^3$  and  $R^{3'}$  are  $R^*$ ,  $R$  or  $=O$ ;  
 $R^4$  and  $R^{4'}$  are  $R^*$ ,  $R$  or  $=O$ ;  
 $R^5$  and  $R^{5'}$  are  $R^*$ ,  $R$  or  $=O$ ; and  
35  $x$  is 0, 1 or 2.

16. A compound according to claim 14 wherein:

A<sup>1</sup> is CR<sup>1</sup>R<sup>1'</sup>, CR<sup>1</sup>, NR<sup>1</sup>, N, O or S; A<sup>2</sup> is CR<sup>2</sup>R<sup>2'</sup>, NR<sup>2</sup> or CR<sup>2</sup>; A<sup>3</sup> is CR<sup>3</sup>R<sup>3'</sup>; A<sup>4</sup> is CR<sup>4</sup>R<sup>4'</sup>, CR<sup>4</sup>, NR<sup>4</sup>, or N; A<sup>5</sup> is CR<sup>5</sup>R<sup>5'</sup>, CR<sup>5</sup>, NR<sup>5</sup>, N, O; D<sup>1</sup> and D<sup>4</sup> are CH; D<sup>2</sup> or D<sup>3</sup> is CH<sup>6</sup>; R<sup>2</sup> or R<sup>4</sup> are R; R<sup>3</sup>, R<sup>3'</sup> and R<sup>5</sup>, R<sup>5'</sup> are =O or R\*, H.

5 17. A compound according to claim 14 wherein:

A<sup>1</sup> is CHR<sup>1</sup>, CR<sup>1</sup>, NR<sup>1</sup>, N or S; A<sup>2</sup> is CR<sup>2</sup> or CR<sup>2</sup>R<sup>2'</sup>; A<sup>3</sup> is CR<sup>3</sup>R<sup>3'</sup>; A<sup>4</sup> is CR<sup>4</sup>R<sup>4'</sup> or NR<sup>4</sup>; A<sup>5</sup> is CR<sup>5</sup>R<sup>5'</sup>; D<sup>1</sup>, D<sup>4</sup> are CH.

18. A compound according to claim 14 wherein:

10 A<sup>1</sup> is CR<sup>1</sup>, A<sup>2</sup> is CR<sup>2</sup>, A<sup>3</sup> is C=O, A<sup>4</sup> is NR<sup>4</sup> and A<sup>5</sup> are CHR<sup>5</sup>.

19. A compound according to claim 14 wherein:

A<sup>1</sup> is NR<sup>1</sup>, A<sup>2</sup> is CHCR<sup>2</sup>, A<sup>3</sup> is CR<sup>3</sup>R<sup>3'</sup>, A<sup>4</sup> is NR<sup>4</sup>, and A<sup>5</sup> are C=O.

15 20. A compound according to claim 14 wherein:

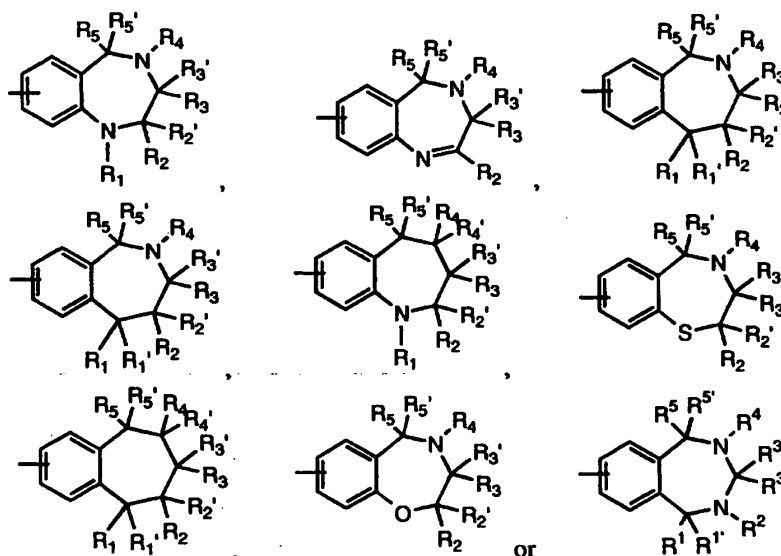
A<sup>1</sup> and A<sup>4</sup> are C=O, A<sup>2</sup> is NR<sup>2</sup>, A<sup>3</sup> is CHR<sup>3'</sup> and A<sup>5</sup> is NR<sup>5</sup>.

21. A compound according to claim 14 wherein:

A<sup>1</sup> is NR<sup>1</sup>, A<sup>2</sup> is CHR<sup>2</sup>, A<sup>3</sup> is C=O, A<sup>4</sup> is NR<sup>4</sup> and A<sup>5</sup> is CHR<sup>5</sup>.

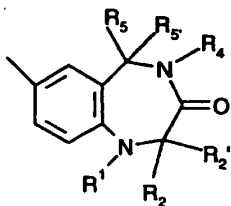
20

22. A compound according to claim 14 wherein:



25

23. A compound according to claim 14 wherein:



24. A compound according to claim 23 wherein:

R<sup>1</sup> is H or C<sub>1-4</sub>alkyl; R<sup>2</sup>, R<sup>2'</sup> are H, -CH<sub>2</sub>CO<sub>2</sub>H; and R<sup>5</sup>R<sup>5'</sup> are H,H.

25. A compound selected from the group of:

- 5-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-aminoacetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(4-phthalimidobutyl)-1H-1,4-benzodiazepine-2-acetic acid;
- 4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetic acid;
- 4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]phenylacetic acid;
- (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-

yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]-carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]-carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetamide;

(±)-2,3,4,5-Tetrahydro-7-[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-4-methyl-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

- (±)-4-[4-[[[(1H-Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoic acid;
- (±)-3-[[[4-(4-Azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoic acid;
- 5 (S)-2,3,4,5-Tetrahydro-7-[[[1-(2-hydroxyethyl)benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- 10 (S)-2,3,4,5-Tetrahydro-7-[[[(4-aminobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-
- 15 acetate;
- (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester;
- 2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;
- 20 (±)-N-[2-(Aminomethyl)-4-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]aspartic acid;
- (±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;
- 25 (±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-4-[4-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoic acid;
- 30 (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate;
- (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[N-[(benzimidazol-2-yl)methyl]-N-[[4-(2-carboxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-
- 35 benzodiazepine-2-acetic acid;
- (±)-2,3,4,5-Tetrahydro-7-[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-



hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate;

5 2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetic acid;

2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic  
10 acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

15 (±)-5-[[2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-yl]methyl]tetrazole;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

20 (±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

25 (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-(N-hydroxy)acetamide;

Ethyl (±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate;

(±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoic  
30 acid;

(±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;

35 2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid; and

(±)-7-[[[(4,5-Dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;  
or pharmaceutically acceptable salts thereof.

- 5 26. A compound selected from the group of:
- 3-[[3-[2-(benzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoic acid;
- 3-{3,4-dihydro-8-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine}-4-propanoic acid;
- 10 3-{4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]}-4-propanoic acid;
- 4-[4-[2-(1H-benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetic acid;
- 1-hydroxy-4-[4-[3-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexaneacetic acid;
- 15 N-[3-[1-[2-(2-Benzimidazolyl)ethyl]carbonyl]piperidinyl]carbonyl]-β-alanine;
- 2-[(Benzimidazol-2-yl)methyl]-5-[2-(carboxy-ethyl)amino]carbonyl]-2,3-dihydro-3-oxo-1H-isoindole;
- [3(R)-[2-(benzimidazol-2-yl)ethyl]-2-oxopiperidinyl]acetyl-3(R)-methyl-β-
- 20 alanine;
- 4-[[[2-(benzimidazolyl)methyl]carbonyl]methylamino]acetyl]phenoxyacetic acid;
- 4-[[[2-(Benzimidazolyl)methyl]carbonyl]methylamino]acetyl]-1,2-phenylenedioxydiacetic acid;
- 25 N-[3-[[[(2-Benzimidazolyl)methyl]carbonyl]amino]benzoyl]-β-alanine;
- [[1-[N-[[[(2-Benzimidazolyl)methyl]carbonyl]tyrosyl]-4-piperidinyl]oxy]acetic acid;
- (S)-4-[[[(2-Benzimidazolyl)methyl]carbonyl]glycyl]-3-methoxycarbonylmethyl-2-oxopiperazine-1-acetic acid;
- 30 (3S,5S)-5-[[4-[(2-Benzimidazolyl)methyl]phenyl]oxymethyl]-3-carboxymethyl-2-pyrrolidinone;
- 1-[(2-Benzimidazolyl)methyl]-3-[4-(2-carboxyethyl)phenyl]-4-methoxy-3-pyrrolin-2-one;
- 2-[6-(benzimidazol-2-yl)methylaminocarbonyl]-1,2,3,4-
- 35 tetrahydroisoquinoliny]acetic acid;
- 2-[6-(benzimidazol-2-yl)methylaminocarbonyl]-1-oxo-1,2,3,4-tetrahydroisoquinoliny]acetic acid;

- 2-[6-((benzimidazol-2-yl)methylcarbonylamino)tetralin]acetic acid;  
2-[6-((benzimidazol-2-yl)methylaminocarbonyl)tetralin]acetic acid;  
2-[5-((benzimidazol-2-yl)methylcarbonylamino)-benzofuran]-propionic acid;  
2-[5-((benzimidazol-2-yl)methylcarbonylamino)-2,3-dihydro-benzofuran]-  
5 propionic acid;  
2-[5-(6-aminopyridinyl-2-methylaminocarbonyl)-benzofuran]-propionic  
acid;  
2-[5-((benzimidazol-2-yl)methylaminocarbonyl)-2,3-dihydro-benzofuran]-  
propionic acid; or  
10 1-[(1H-benzimidazol-2-yl)methyl]-3-{4[(2-ethoxycarbonyl)ethyl]}phenyl]-3-  
oxo-imidazolidine;  
or pharmaceutically acceptable salts thereof.

27. A pharmaceutical composition which comprises a pharmaceutically acceptable  
15 carrier and a compound according to any one of claims 1-26.

28. A method of inhibiting a vitronectin receptor in a mammal which comprises  
administering an effective amount of a compound according to formula (I) or (II) or  
(III) or (IV) or (V) as defined in claim 1.

29. A method according to claim 28 wherein the compound inhibits the vitronectin  
receptor with a  $K_i$  at the vitronectin receptor that is ten-fold greater than the  $K_i$  for  
said compound at the fibrinogen receptor.

30. A method according to claim 28 wherein the compound inhibits the vitronectin  
receptor with a  $K_i$  at the vitronectin receptor that is thirty-fold greater than the  $K_i$  for  
said compound at the fibrinogen receptor.

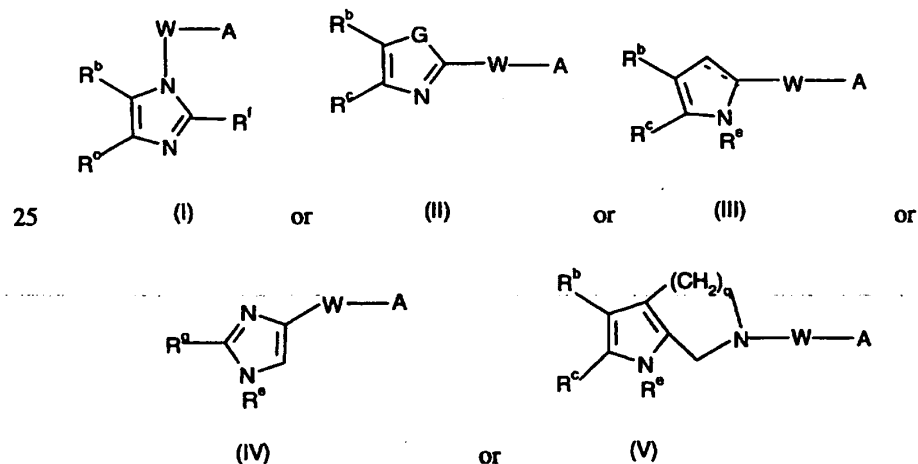
31. A method according to claim 28 wherein the compound inhibits the vitronectin  
30 receptor with a  $K_i$  at the vitronectin receptor that is a hundred-fold greater than the  
 $K_i$  for said compound at the fibrinogen receptor.

32. A method according to claim 28 for treating diseases wherein bone resorption is  
a factor.

33. A method according to claim 28 for treating osteoporosis, inflammation,  
35 restenosis or atherosclerosis.

34. A method of inhibiting a vitronectin receptor in a mammal which comprises administering an effective amount of a compound according to formula (XXI) or (XXII) as defined in claim 13.
- 5 35. A method according to claim 34 wherein the compound inhibits the vitronectin receptor with a  $K_i$  at the vitronectin receptor that is ten-fold greater than the  $K_i$  for said compound at the fibrinogen receptor.
- 10 36. A method according to claim 34 wherein the compound inhibits the vitronectin receptor with a  $K_i$  at the vitronectin receptor that is thirty-fold greater than the  $K_i$  for said compound at the fibrinogen receptor.
- 15 37. A method according to claim 34 wherein the compound inhibits the vitronectin receptor with a  $K_i$  at the vitronectin receptor that is a hundred-fold greater than the  $K_i$  for said compound at the fibrinogen receptor.
- 20 38. A method according to claim 34 for treating diseases wherein bone resorption is a factor.
39. A method according to claim 34 for treating osteoporosis, inflammation, restenosis or atherosclerosis.
- 25 40. A method of inhibiting a vitronectin receptor in a mammal which comprises administering an effective amount of a compound according to claim 25.
- 30 41. A method according to claim 40 wherein the compound inhibits the vitronectin receptor with a  $K_i$  at the vitronectin receptor that is ten-fold greater than the  $K_i$  for said compound at the fibrinogen receptor.
42. A method according to claim 40 wherein the compound inhibits the vitronectin receptor with a  $K_i$  at the vitronectin receptor that is thirty-fold greater than the  $K_i$  for said compound at the fibrinogen receptor.
- 35 43. A method according to claim 40 wherein the compound inhibits the vitronectin receptor with a  $K_i$  at the vitronectin receptor that is a hundred-fold greater than the  $K_i$  for said compound at the fibrinogen receptor.

44. A method according to claim 40 for treating diseases wherein bone resorption is a factor.
- 5 45. A method according to claim 40 for treating osteoporosis, inflammation, restenosis or atherosclerosis.
46. The use of a compound according to any one of claims 1-26 in the manufacture of a medicament.
- 10 47. The use of a compound according to any one of claims 1-26 in the manufacture of a medicament for the inhibition of the vitronectin receptor in a mammal in need thereof.
- 15 48. The use of a compound according to any one of claims 1-26 in the manufacture of a medicament for the treatment of diseases in which bone resorption is a factor.
49. The use of a compound according to any one of claims 1-26 in the manufacture of a medicament for the treatment of osteoporosis, inflammation, restenosis, or
- 20 atherosclerosis.
50. A process for preparing a compound of the formula (I) or (II) or (III) or (IV) or (V):



wherein:

W is - (CHR<sup>g</sup>)<sub>b</sub>-V'- or phenyl;

A is a fibrinogen receptor antagonist template;

V' is CONR<sup>21</sup> or NR<sup>21</sup>CO;

G is NR<sup>e</sup>, S or O;

5 R<sup>g</sup> is H, C<sub>1-6</sub>alkyl, Het-C<sub>0-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>0-6</sub>alkyl or Ar-C<sub>0-6</sub>alkyl;

R<sup>21</sup> is Het-(CH<sub>2</sub>)<sub>0-6</sub>-U'-(CH<sub>2</sub>)<sub>1-6</sub>-, C<sub>3-7</sub>cycloalkyl-(CH<sub>2</sub>)<sub>0-6</sub>-U'-(CH<sub>2</sub>)<sub>1-6</sub>-, or

Ar-(CH<sub>2</sub>)<sub>0-6</sub>-U'-(CH<sub>2</sub>)<sub>1-6</sub>-;

U' is CONR<sup>f</sup> or NR<sup>f</sup>CO;

R<sup>f</sup> is H, C<sub>1-6</sub>alkyl or Ar-C<sub>1-6</sub>alkyl;

10 R<sup>e</sup> is H, C<sub>1-6</sub>alkyl, Ar-C<sub>1-6</sub>alkyl, Het-C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl-C<sub>1-6</sub>alkyl,

(CH<sub>2</sub>)<sub>q</sub>OH or (CH<sub>2</sub>)<sub>k</sub>CO<sub>2</sub>R<sup>g</sup>;

k is 0, 1 or 2;

q is 1 or 2;

b is 0, 1 or 2;

15 R<sup>b</sup> and R<sup>c</sup> are independently selected from H, C<sub>1-6</sub>alkyl, Ar-C<sub>0-6</sub>alkyl, Het-

C<sub>0-6</sub>alkyl, or C<sub>3-6</sub>cycloalkyl-C<sub>0-6</sub>alkyl, halogen, CF<sub>3</sub>, OR<sup>f</sup>, S(O)<sub>k</sub>R<sup>f</sup>, COR<sup>f</sup>,

NO<sub>2</sub>, N(R<sup>f</sup>)<sub>2</sub>, CO(NR<sup>f</sup>)<sub>2</sub>, CH<sub>2</sub>N(R<sup>f</sup>)<sub>2</sub>, or R<sup>b</sup> and R<sup>c</sup> are joined together to

form a five or six membered aromatic or non-aromatic carbocyclic or

heterocyclic ring, optionally substituted by up to three substituents chosen

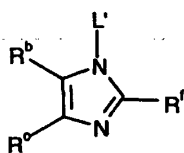
20 from halogen, CF<sub>3</sub>, C<sub>1-4</sub>alkyl, OR<sup>f</sup>, S(O)<sub>k</sub>R<sup>f</sup>, COR<sup>f</sup>, CO<sub>2</sub>R<sup>f</sup> OH, NO<sub>2</sub>,

N(R<sup>f</sup>)<sub>2</sub>, CO(NR<sup>f</sup>)<sub>2</sub>, and CH<sub>2</sub>N(R<sup>f</sup>)<sub>2</sub>, or methylenedioxy;

or a pharmaceutically acceptable salt thereof,

which process comprises:

25 (i) for formula (I) compounds, reacting a compound of the formula (Ia) with a compound of formula (Ib):



(Ia)

L<sup>f</sup>-A

(Ib)

30

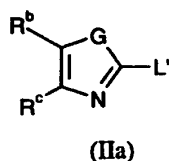
wherein:

$R^b$ ,  $R^c$ ,  $R^f$ , and A are as defined in formula (I), with any reactive functional groups protected; and

5  $L'$  and  $L''$  are groups which react to form an amide bond in the moiety W or  $L'$  is phenyl substituted by  $-\text{SnBu}_3$ , and  $L''$  is halo;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt; or

10 (ii) for formula (II) compounds, reacting a compound of the formula (IIa) with a compound of the formula (Ib):



$L''$ -A  
(Ib)

15

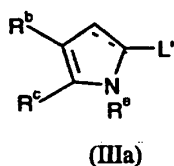
wherein:

$R^b$ ,  $R^c$ , G and A are as defined in formula (I), with any reactive functional groups protected; and

20  $L'$  and  $L''$  are groups which react to form an amide bond in the moiety W or  $L'$  is phenyl substituted by  $-\text{SnBu}_3$ , and  $L''$  is halo;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt; or

25 (iii) for formula (III) compounds, reacting a compound of the formula (IIIa) with a compound of the formula (Ib):



$L''$ -A  
(Ib)

30 wherein:

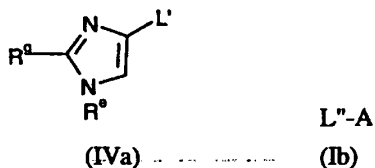
$R^b$ ,  $R^c$ ,  $R^e$ , and A are as defined in formula(I), with any reactive functional groups protected; and

$L'$  and  $L''$  are groups which react to form an amide bond in the moiety W or

L' is phenyl substituted by -SnBu<sub>3</sub>, and L'' is halo;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt; or

- 5 (iv) for formula (IV) compounds, reacting a compound of the formula (IVa) with a compound of the formula (Ib):



10

wherein:

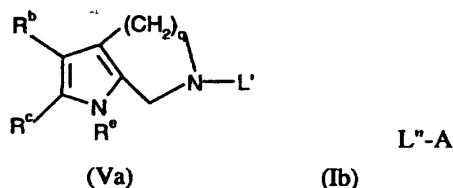
R<sup>a</sup>, R<sup>b</sup>, and A are as defined in formula(I), with any reactive functional groups protected; and

L' and L'' are groups which react to form an amide bond in the moiety W or

- 15 L' is phenyl substituted by -SnBu<sub>3</sub>, and L'' is halo;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt; or

- (v) for formula (V) compounds, reacting a compound of the formula (Va) with a compound of the formula (Ib):



- 25 wherein:

R<sup>a</sup>, R<sup>b</sup>, and A are as defined in formula(I), with any reactive functional groups protected; and

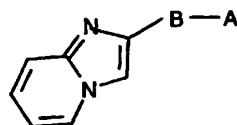
L' and L'' are groups which react to form an amide bond in the moiety W or

L' is phenyl substituted by -SnBu<sub>3</sub>, and L'' is halo;

- 30 and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

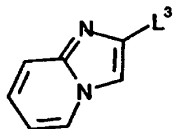


51. A process for preparing a compound of the formula (XXI):



(XXI)

5 wherein A and B are as defined in claim 13,  
which process comprises reacting a compound of the formula (XXV) with a  
compound of the formula (XXVI):



(XXV)



(XXVI)

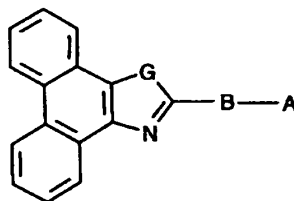
wherein:

A is as defined in claim 13, with any reactive functional groups protected;

and

15 L<sup>3</sup> and L<sup>4</sup> are groups which react to form a covalent bond in the moiety B;  
and thereafter removing any protecting groups, and optionally forming a  
pharmaceutically acceptable salt.

52. A process for preparing a compound of the formula (XXI):

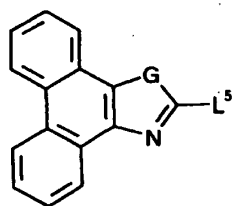


(XXII)

wherein A, B and G are as defined in claim 13,

which process comprises reacting a compound of the formula (XXVII) with a

25 compound of the formula (XXVIII):



(XXVII)

L<sup>6</sup>-A

(XXVIII)

5 wherein:

A and G are as defined hereinabove, with any reactive functional groups protected; and

L<sup>5</sup> and L<sup>6</sup> are groups which react to form a covalent bond in the moiety B;  
and thereafter removing any protecting groups, and optionally forming a

10 pharmaceutically acceptable salt.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/20748

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) : Please See Extra Sheet. US CL : 514/221; 540/513 According to International Patent Classification (IPC) or to both national classification and IPC																				
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/221; 540/513  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE																				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>																				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																		
A	US 3,627,754 A (NING ET AL.) 14 December 1971(14.12.71), see entire document, especially column 1.	1-52, parts																		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																				
<table border="0"><tr><td>* Special categories of cited documents:</td><td>"T"</td><td>later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td></tr><tr><td>"A" document defining the general state of the art which is not considered to be of particular relevance</td><td>"X"</td><td>document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td></tr><tr><td>"E" earlier document published on or after the international filing date</td><td>"Y"</td><td>document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td></tr><tr><td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td><td>"Z"</td><td>document member of the same patent family</td></tr><tr><td>"O" document referring to an oral disclosure, use, exhibition or other means</td><td></td><td></td></tr><tr><td>"P" document published prior to the international filing date but later than the priority date claimed</td><td></td><td></td></tr></table>			* Special categories of cited documents:	"T"	later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z"	document member of the same patent family	"O" document referring to an oral disclosure, use, exhibition or other means			"P" document published prior to the international filing date but later than the priority date claimed		
* Special categories of cited documents:	"T"	later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention																		
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"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art																		
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z"	document member of the same patent family																		
"O" document referring to an oral disclosure, use, exhibition or other means																				
"P" document published prior to the international filing date but later than the priority date claimed																				
Date of the actual completion of the international search 04 MARCH 1997		Date of mailing of the international search report 21 MAR 1997																		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer ROBERT W. RAMSUER <i>Jab</i> Telephone No. (703) 308-1231																		

Form PCT/ISA/210 (second sheet)(July 1992)\*

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/20748**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-52, parts  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Please See Extra Sheet.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/20748

## A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

A61K 31/40; C07D 487/04

## BOX 1. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

### 2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. W, A, V', G Ra, the provisos, the formulae, etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed does not contain a single technical feature as note the many formulae (e.g. I, II, III, etc.). Therefore, the first discernable invention as found in Example 1, the compound therein, the pharmaceutical composition therewith, the method of preparation thereof and the method of treating osteoporosis therewith has been searched.